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Amesthesia (y) and Analgesia

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The Logical Choice

P, 24, 545



Consider the Critical Parameters in Selecting a Neuromuscular Blocking Agent

	Norcuron® (vecuronium bromide) for injection
HEMODYNAMICS	Hemodynamic stability with no statistically significant variations in blood pressure, cardiac output, or systemic vascular resistance. 1,2
HISTAMINE	Clinical evidence indicates that reactions commonly associated with histamine release are unlikely to occur at doses up to 0.28 mg/kg. ¹⁻⁴
DURATION OF ACTION (0.08–0.1 mg/kg)	25–30 minutes (under balanced anesthesia).
DOSING FLEXIBILITY	Offers superior flexibility in long procedures: continuous infusion or high initial bolus dose. 5 "one can preselect a dose of vecuronium to produce either a short, medium, or long-acting degree of neuromuscular blockade without cardiovascular side effects." 6
SŢORAGE	Room temperature. No refrigeration required.
SHELF LIFE	2 years in lyophilized form.

Morcuron

(vecuronium bromide) for injection

The Logical Choice for Neuromuscular Blockade

See following page for brief summary of prescribing information.



ORGANON INC. WEST ORANGE

Norcuron^{*} (vecuronium bromide) for injection

Before prescribing, please consult complete product information, a summary of which follows

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZAROS.

CONTRAINDICATIONS: Norcuron* is contraindicated in patients known to have a hypersensitivity to it.
WARNINGS: NORCURON* SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT
MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION,
ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN
MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. In patients who are known to have myasthenia gravis or the
myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron* may have profound effects. In such patients, a peripheral
nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle

relaxants

PRECAUTIONS: General: Limited data on histamine assay and available clinical experience indicate that hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other reactions commonly associated with histamine release are unlikely to occur.

Renal Failure: Norcuron® is well tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockade may occur; therefore, if anephric patients cannot be prepared for non-elective surgery a lower initial dose of Norcuron® should be considered.

Attered Circulation Time: Conditions associated with slower circulation time in cardiovascular disease, old age, edematous states resulting in increased volume of distribution may contribute to a delay in onset time, therefore dosage should not be increased.

states resulting in increased volume of distribution may contribute to a deay in onset time, therefore dosage should not be increased.

Hepatic Disease: Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in Norcuron* metabolism and excretion. Data currently available do not permit dosage recommendations in patients with impaired liver function. Long-term Use in L.C.U. In the intensive care unit, in rare cases, long-term use of neuromuscular blocking drugs to facilitate Long-term Use in L.C.U. In the intensive care unit, in rare cases, long-term use of neuromuscular blocking drugs to facilitate mechanical ventilation may be associated with prolonged paralysis and/or skeletal muscle weakness that may be first noted mechanical ventilation may be associated with prolonged paralysis and/or skeletal muscle weakness that may be first noted mechanical ventilation as provided in the properties of the propertie

Severe Obesity or Neuromuscular Disease: Patients with severe obesity or neuromuscular disease may pose airvay and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron* Malignant Hyperthermia: Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially datal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron* is capable of triggering malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron* is capable of triggering malignant hyperthermia. C. N.S.: Norcuron* has no known effect on consciousness, the pain threshold or cerebration. Administration must be accompanied by adequate anesthesia or sedation.

Drug Interactions: Pior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron* of Norcuron* should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.4-0.40 Gm/kg of Norcuron* may be administered to produce complete neuromuscular block with clinical duration of action of 25-30 minutes. The use of Norcuron* before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied.

Other nondepolarizing nenpetitive muscle relaxants in the same patient.

Other nondepolarizing nenpetitive muscle relaxants in the same patient.

Inhalational Anesthetics: Use of volatile inhalational anesthetics with Norcuron* will enhance neuromuscular blockade.

Potentiation is most prominent with use of enflurane and instrument. With the above agents the initial dose of Norcuron* may be the same as with balanced anesthesia unless the inhalational anesthetics with Norcuron* will enhance neuromuscular blockade.

Inhalational Anesthetic

in intensity of blockade or duration of action of Norcuron* is noted from the use of intilocationates, hallowed also cause introus oxide, or droperidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

Prolonged paralysis and/or skeletal muscle weakness have been reported after long-term use to support mechanical ventilation in the intensive care unit. (see PRECAUTIONS).

Bronchospasm, flushing, redness, hypotension and tachycardia have been reported in very rare instances.

OVERDOSAGE: The possibility of latrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation.

Excessive doses of Norcuron* produce enhanced pharmacological effects. Residual neuromuscular blockage beyond the time period needed may occur with Norcuron* as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulation may be used to muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimular may be used to muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimular may be used to muscle weakness, decreased respiratory reserve.

Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narotics, thiobarbiturates and other central nervous system depressants. Under such circumstances, the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normit respiration is assured. Regnonle* (pyridostigmine bromide) injection, neostigmine, or derophonium, in conjunction with respiration is assured. Regnonle* (pyridostigmine bromide) injection, neostigmine, or derophonium, in conjunction with respiration is assured. Regnonle* (pyridostigmine bromide) for prompt reversal (within 30 minutes) may occur in the p

anesthetics and by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. To obtain maximum clinical benefits of Norcuron* and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron* is 0.0 80 to 0.10 mg kg (1.4 to 1.75 times the ED₉₀) given as an intravenous bobus injection. This dose can be expected to produce good or excellent non-emergency intubation conditions in 2.5 to 3 minutes after injection. Under balanced anesthesia, clinically required neuroriuscular blockade lasts approximately 25-30 minutes after injection. Under balanced anesthesia, clinically required neuroriuscular blockade lasts approximately 25-50 or control achieved approximately 45-65 minutes after injection. In the presence of potent inhalation anesthetics, the neuroriuscular blocking effect of Norcuron* is enhanced. If Norcuron* is first administered more than 5 minutes after the start of inhalation agent or when steady state has been achieved, the initial Norcuron* dose may be reduced by approximately 15%, i.e. 0.060 to 0.085 mg/kg.

Prior administration of succinylcholine may enhance the neuroriuscular blocking effect and duration of action of Norcuron*. If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron* to 0.04-0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.05 mg/kg volume to 1.00 mg/kg v

carded. Infusion rates of Norcuron® can be individualized for each patient using the following table:

Drug Delivery Rate		Delivery Rate
(μg/kg/min)	0.1 mg/mL* (mL/	kg/min) 0.2 mg/mL†
0.7 0.8 0.9 1.0 1.1 1.2	0.007 0.008 0.009 0.010 0.011 0.011 0.012 0.013	0.0035 0.0040 0.0045 0.0050 0.0055 0.0060 0.0065

10 mg of Norcuron in 100 mL solution †20 mg of Norcuron* in 100 mL solution

The following table is a guideline for mL/min delivery for a solution of 0.1 mg/mL (10 mg in 100 mL) with an infusion pump. NORCURON® INFUSION RATE — mL/MIN

Amount of Drug			Pati	ent Weight -	- kg		
μg/kg/min	40	50	60	70	80	90	100
0.7 0.8 0.9	0.28 0.32 0.36 0.40	0.35 0.40 0.45 0.50	0.42 0.48 0.54 0.60	0.49 0.56 0.63 0.70	0.56 0.64 0.72 0.80	0.63 0.72 0.81 0.90 0.99	0.70 0.80 0.90 1.00 1.10
1 1 1 2 1 3	0.44 0.48 0.52	0.55 0.60 0.65	0.66 0.72 0.78	0.77 0.84 0.91	0.88 0.96 1.04	1.08 1.17	1.20

NOTE: If a concentration of 0.2 mg/mL is used (20 mg in 100 mL), the rate should be decreased by one-half.

Dosage in Children: Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg) a adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial diand may also require supplementation slightly more often than adults. Intants under one year of age but older than 7 v are moderately more sensitive to Norcuron* on a mg/kg basis than adults and take about 1½ times as long to recover also subsection of PRECAUTIONS titled Pediatric Use. Information presently available does not permit recommendatio usage in neonates (see PRECAUTIONS). There are insufficient data concerning continuous infusion of vecuronium in therefore, no dosing recommendation can be made.

COMPATIBILITY: Norcuron* is compatible in solution with:

0.9% NaCl solution

5% glucose in water

5% glucose in water
5% glucose in water
Sterile water for injection
Use within 24 hours of mixing with the above solutions.
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administrations.

whenever solution and container permit. STORAGE: 15-30°C (59-86°F). Protect from light

- When reconstituted with supplied bacteriostatic water for injection: CONTAINS BENZYL ALCOHOL, WHICH IS NO INTENDED FOR USE IN NEWBORNS. Use within 5 days. May be stored at room temperature or refrigerated. When reconstituted with sterile water for injection or other compatible I.V. solutions: Refrigerate vial. Use within . Single use only. Discard unused portion.

References:

- Norcuron® (vecuronium bromide) for injection package insert.
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Books for review should be sent directly to: Book Review Editor, Norig Ellison, MD, Department of Anesthesia, University of Pennsylvania,

FOR SHORTER **SURGICAL** PROCEDURES:

*As with all potent opioids, appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained. established and flaminance.
The duration and degree of respiratory depression and increased alrway resistance usually increase with dose, but have also been observed at lower doses. Because of the possibility of delayed respiratory depression, monitoring of the patient must continue well after surgery.



enta (alfentanil HCI) Injection (1)

For moment-to-moment control of stress responses

PID ON

Rapidly blocks sympathetic responses to induction and intubation

T DUR

Results in quick recovery of consciousness*

COI

Postoperative respiratory depression is of short duration*

Before prescribing, please consult complete prescribing information, of which the following is a brief summary.

CAUTION: Federal Law Prohibits Dispensing Without Prescription
DESCRIPTION: ALFENTA is a sterile, non-pyrogenic, preservative free aqueous solution containing alfentanil
hydrochloride equivalent to 500 µg per ml of alfentanil base for intravenous injection. The solution, which contains
sodium chloride for isotonicity, has a pH range of 4.0-6.0.
CONTRAINDICATIONS: ALFENTA (alfentanil hydrochloride) is contraindicated in patients with known hypersensitivity to the druin

INFORMATION: ALPENTA is a sterile, non-pyrogenic, preservative riee aqueous soution containing arentain hydrochloride equivalent to 500 up per mil of alentanih base for intravenous injection. The solution, which contains sodium chloride by instonative, has a pit range of 4.0-6.0.

CONTRAINDICATIONS: ALFENTA (altentanii hydrochloride) is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: ALFENTA SHOULD BE ADMINISTERED DNIY BY PERSONS SPECIFICALLY TRAINED IN THE USE OF INTRAVENOUS AND GENERAL ANESTHETIC AGENTS AND IN THE MANAGEMENT OF RESPIRATORY EFFECTS OF INTRAVENOUS AND GENERAL ANESTHETIC AGENTS AND IN THE MANAGEMENT OF RESPIRATORY EFFECTS OF POTENT OPIDIOS. AN OPIDIO ANTACONIST, RESUSCITATIVE AND INTUBATION EQUIPMENT AND OXYGEN SHOULD POTENT OPIDIOS. AN OPIDIO ANTACONIST, RESUSCITATIVE AND INTUBATION EQUIPMENT AND OXYGEN SHOULD POTENT OPIDIOS. AND POTENT OPIDIOS. AND POTENT AND EXPENSION MONITORING OF THE PATENT MUSIC CONTINUE WELL AFTER SURGERY ALFENTA (altentanii hydrochloride) administered in Or THE PATENT MUSIC CONTINUE WELL AFTER SURGERY ALFENTA (altentanii hydrochloride) administered in oritical dosages up to 20 µg/kg any cause skeletal muscle rigidity particularly of the truncal muscles. The incidence and severity of muscle rigidity is usually dose-related. Administration of LFENTA at ansesthetic induction dosages and severity of muscle rigidity is usually dose-related. Administration of LFENTA at dosages up to muscles, including those of the neck and extermities. The incidence may be reduced by: 1) routine methods of muscles including those of the neck and extermities. The incidence may be reduced by: 1) routine methods of muscles including those of the neck and extermities. The incidence may be reduced by: 1) routine methods of muscles including those of the neck and extermities. The incidence may be reduced by: 1) routine methods of muscles including the particular of the neck and extermities. The incidence of the neck and extermities and particular of the administration

respiration. When the continuous process and process and the continuous process and process and prolong recovery.

Perioperative administration of drugs affecting hepatic blood flow or enzyme function may reduce prasina clear and prolong recover.

Perioperative administration of drugs affecting hepatic blood flow or enzyme function may reduce prasina clear and prolong recovers.

Mutagenesis and impairment of Fertility: No long-term animal studies of ALFENTA have Carcinogenic potential. The micronucleus test in female rats and the dominant tethal been performed to evaluate carcinogenic potential. The micronucleus test in female rats and proposed the provided produced no structural chromosome mutations or induction of dominant lethal volutions the upper human dose) produced no structural chromosome mutations or induction of dominant lethal volutions. The Ames Salmonella typhimurum metabolic activating test also revealed no mutagenic activity.

Pregnancy Category C: ALFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects could have been due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects has been observed after administration of ALFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. ALFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of ALFENTA in labor and delivery. Placental transfer of the drug has been reported; therefore, use in labor and delivery is not recommended.

Nursing Mothers: in one study of nine women undergoing post-partum tubal ligation, significant levels of ALFENTA were detected in colostrum four hours after administration of 60 µg/kg of ALFENTA, with no detectable levels present after 28 hours. Caution should be exercised when ALFENTA is administered to a nursing woman. Pediatric Use: Adequate data to support the use of ALFENTA in children under 12 years of age are not presently

available.

ADVENSE REACTIONS: The most common adverse reactions, respiratory depression and skeletal muscle rigidity, are extensions of known pharmacological effects of opioids. See CLINICAL PHARMACOLOGY, WARNINGS and are extensions of known pharmacological effects of opioids. See CLINICAL PHARMACOLOGY, WARNINGS and are extensions of known pharmacological effects of opioids. See CLINICAL PHARMACOLOGY, WARNINGS and prescription of the properties of the properties of the properties of the properties of the depression, respiratory arrest, pradycardia, asystole, arrhythmias and hypotension have also been reported. The depression, respiratory arrest, pradycardia, asystole, arrhythmias and hypotension have also been reported. The controlled trials involved treatment comparisons trials involving 1183 patients, of whom 785 received ALFENTA. The controlled trials involved treatment comparisons with fentanyl, thiopentals odium, enflurane, saline placebo and halothane. Incidences are based on disturbing and mondisturbing adverse reactions reported. The comparative incidence in clinical trials of alfentanii induction, and by type of use, e.g., chest wall rigidity has a higher reported incidence in clinical trials of alfentanii induction, and by the type of surgery, e.g., nausea and vomiting have a higher incidence in patients undergoing gynecologic surgery.

Percent	ALFENTA (N = 785)	Fentanyl (N = 243)	Thiopentai Sodium (N = 66)	Enflurane (N = 55)	Haiothane (N = 18)	Saline Placebo
Gastrointestinal Nausea Vomiting	28 18	44 31	14 11	5 9	0 13	22 17
Cardiovascular Bradycardia Tachycardia Hypotension Hypertension Arrhythmia	14 12 10 18 2	7 12 8 13	8 39 7 30 5	0 36 7 20 4	0 31 0 6 6	0 11 0 0
Musculoskeletal	17	12	0	0	0	0
Chest Wall Rigidity Skeletal Muscle Movements	6	2	6	2	0	0
Respiratory Apnea Postoperative Respiratory Depression	7 2	0	0	0	0	0
CNS Dizziness Sleepiness/ Postoperative	3 2	5 8	0 2	0	0	0 6
Sedation	2	2	0 ented balanced barbiti	0	0 ovide anesth	0 esia and one in

*From two clinical trials, one involving supplemented balanced barbiturate / nitrous oxide anesthesia and one in healthy volunteers who did not undergo surgery.

healthy volunteers who did not undergo surgery.

In addition, other adverse reactions less frequently reported (1% or less) were: Laryngospasm, bronchospasm, postoperative confusion, headache, shivering, postoperative euphoria, hypercarbia, pain on injection, urticaria, and itching. Some degree of skeletal muscle rigidity should be expected with induction doses of ALFENTA and itching. Some degree of skeletal muscle rigidity should be expected with induction doses of ALFENTA publications. The provided forgospath in the proprinciple of the substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

DYENDOSABE: Overdosage would be manifested by extension of the pharmacological actions of ALFENTA (alfentanii hydrochloride) (see CLINICAL PHARMACOLOGY) as with other potent opticid analgesics. No experience of (alfentanii hydrochloride) (see CLINICAL PHARMACOLOGY) as with other potent opticid analgesics. No experience of overdosage with ALFENTA was reported during clinical trais. The intravenous LO₈₀ of ALFENTA is 43.0-50.9 mg/kg in rats, 72.2-73.6 mg/kg in mice, 71.8-81.9 mg/kg in guinea pigs and 59.5-87.5 mg/kg in dogs. Intravenous administration of an optical analgonists such as naloxone should be employed as a specific antidote to manage respiratory depression following overdosage with ALFENTA may be longer than the duration of respiratory depression following overdosage with ALFENTA may be longer than the duration of action of the optical antagonist. Administration of an optical analgonists should not preclude immediate establishment of a patent airway, administration of oxygen, and assisted or controlled ventilation as indicated for hypoventilation or apnea. If respiratory depression is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled ventilation. Intravenous fluids and vasoactive agents may be required to facilitate assisted or controlled ventilation. Intravenous fluids and vasoactive a

agent may be required to facilitate assisted or controlled ventilation. Intravenous fluids and vasoactive agents where required to manage hemodynamic instability.

DOSABE AND ADMINISTRATION: The dosage of ALFENTA (alfentanii hydrochloride) should be individualized in each patient according to body weight, physical status, underlying pathological condition, use of other drugs, and type and duration of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. The dose of ALFENTA should be determined on the basis of lean body weight. The dose of ALFENTA should be reduced in elderly or debilitated patients (see PRECAUTIONS). Vital signs should be monitored routinely. Protect from light. Store at room temperature 15°-30° C (59°-86° F).

Manufactured by Taylor Pharmacal Co. for



March 1987, April 1988 U.S. Patent No. 4,167,574 49-7619902-M

Piscataway, N.J. 08854

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Anesthesia and Analgesia

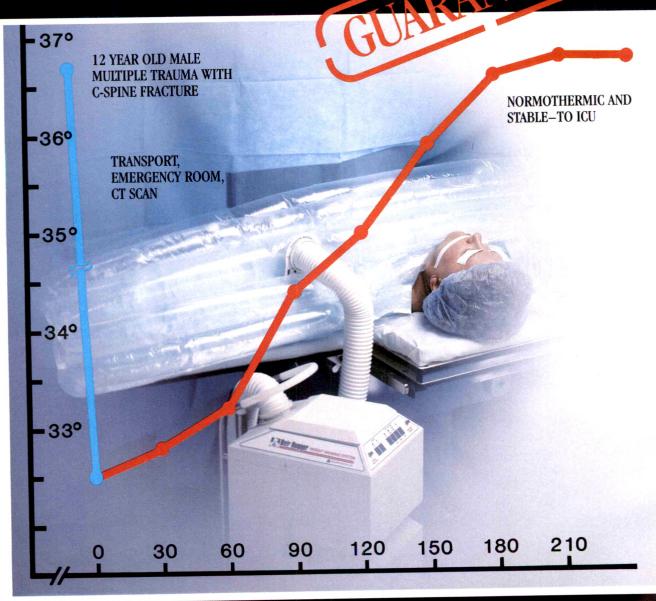
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Amesthesia and Analgesia



Journal of the International Anesthesia Research Society

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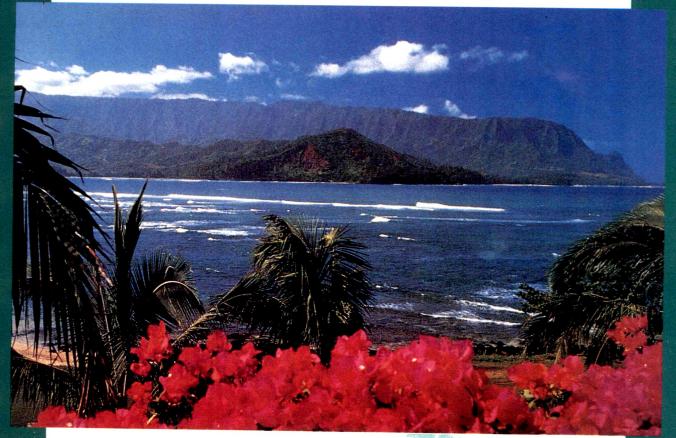
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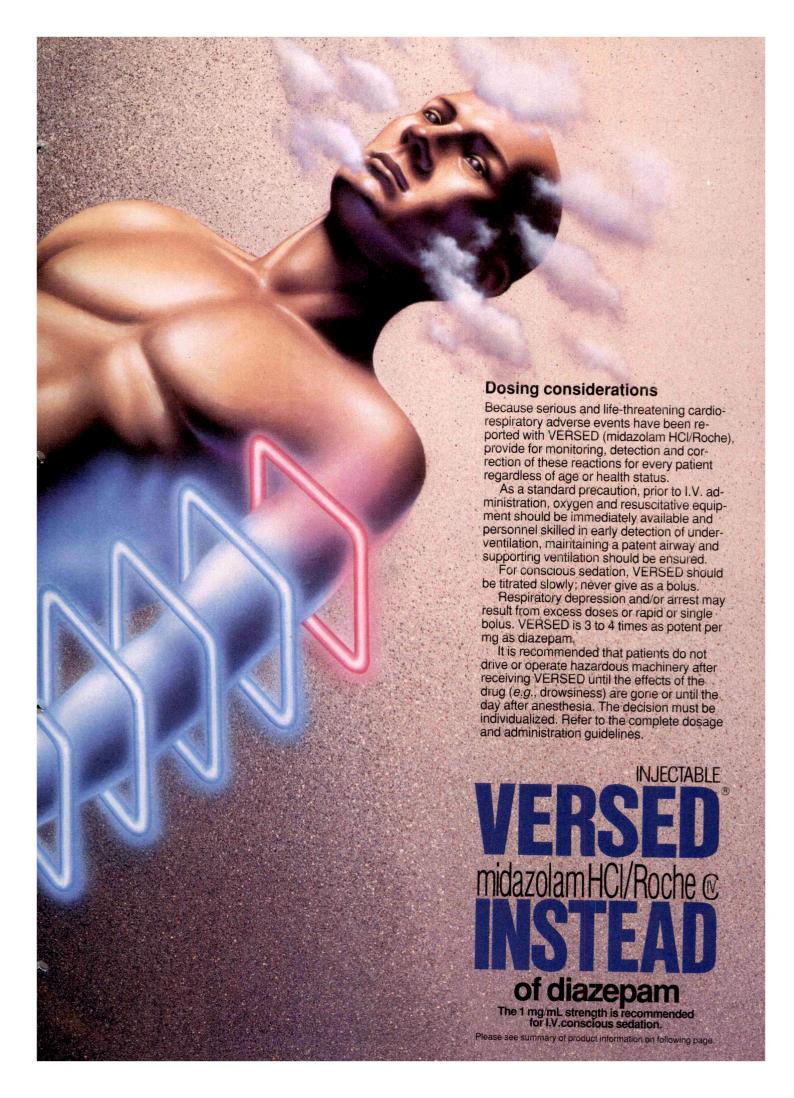
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VERSED* (midazolam HCI/Roche) ® NJECTION

Before prescribing, please consult complete product information, a summary of which follows:

Intravenous VERSED has been associated with respiratory depression and respiratory arrest, especially when used for conscious sedation. In some cases, where this was not recognized promptly and treated effectively, death or hypoxic encephalopathy has resulted. Intravenous VERSED should be used only in hospital or ambulatory care settings, including physicians' offices, that provide for continuous monitoring of respiratory and cardiac function. Immediate availability of resuscitative drugs and equipment and personnel trained in their use should be assured (See WARNINGS.) assured. (See WARNINGS.)
The initial intravenous dose for conscious sedation may be as little as 1 mg.

The initial intravenous dose for conscious sedation may be as little as 1 mg, but should not exceed 2.5 mg in a normal healthy adult. Lower doses are necessary for older (over 60 years) or debilitated patients and in patients receiving concomitant narcotics or other CNS depressants. The initial dose and all subsequent doses should never be given as a bolus; administer over at least 2 minutes and allow an additional 2 or more minutes to fully evaluate the sedative effect. The use of the 1 mg/mL formulation or cilution of the 1 mg/mL or 5 mg/mL formulation is recommended to facilitate slower injection. Consult complete product information under DOSAGE AND ADMINISTRATION for complete dosing information.

CONTRAINDICATIONS: Patients with known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma; may be used in open angle glaucoma only if patients are receivtherapy WARNINGS: Never use without individualization of dosage. Prior to IV

WARNINGS: Never use without individualization of dosage. Prior to IV use in any dose, ensure immediate availability of oxygen, resuscitative equipment and skilled personnel for maintenance of a patent airway and support of ventilation. Continuously monitor for early signs of underventilation or apnea, which can lead to hypoxia/cardiac arrest unless effective countermeasures are taken immediately. Vital signs should continue to be monitored during the recovery period. Because IV VERSED depresses respiration, and opioid agonists and other sedatives can add to this depression, it should be administered as an induction agent only by a person trained in general anesthesia and should be used for conscious sedation only in the presence of personnel skilled in early detection of underventilation, maintaining a patent airway and supporting ventilation. For conscious sedation, do not administer IV by rapid or single bolus. Serious cardiorespiratory adverse events have occurred. These have included respiratory depression, apnea, respiratory arrest and/or cardiac arrest, sometimes resulting in death. There have been rare reports of hypotensive episodes requiring treatment during or after diagnostic or surgical manipulations in patients who have received VERSED. Hypotension occurred more frequently in the conscious sedation studies in patients premedicated with narcotic. Reactions such as agitation, involuntary movements, hyperactivity and combativeness have been reported. These may be due to inadequate or excessive dosing or improper administration; however, the possibility of cerebral hypoxia or true paradoxical reactions should be considered. Should these reactions occur, response to each dose of VERSED and all other drugs should be evaluated before proceeding.

hypoxia or true paradoxical reactions should be considered. Should these reactions occur, response to each dose of VERSED and all other drugs should be evaluated before proceeding. Concomitant use of barbiturates, alcohol or other CNS depressants may increase the risk of underventilation or apnea and may contribute to profound and/or prolonged drug effect. Narcotic premedication also depresses the ventilatory response to carbon dioxide stimulation. Higher risk surgical, elderly or debilitated patients require lower dosages for induction of anesthesia, premedicated or not. Patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effect of VERSED. Patients with chronic renal failure and patients with congestive heart failure eliminate midazolam more slowly. Because elderly patients frequently have inefficient function of one or more organ systems, and because dosage requirements have been shown to decrease with age, reduce initial dosage and consider possibility of a profound and/or prolonged effect.

Do not administer in shock, coma, acute alcohol intoxication with depression

Do not administer in shock, coma, acute alcohol intoxication with depression of vital signs. Particular care should be exercised in the use of IV VERSED in patients with uncompensated acute illnesses, such as severe fluid or electrolyte disturbances

Guard against unintended intra-arterial injection; hazards in humans

Guard against unintended intra-arterial injection; hazards in furnalis unknown. Avoid extravasation. Gross tests of recovery from the effects of VERSED cannot alone predict reaction time under stress. This drug is never used alone during anesthesia, and the contribution of other perioperative drugs and events can vary. The decision as to when patients may engage in activities requiring mental alertness must be individualized; it is recommended that no patient should operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until the day after anesthesia, whichever is longer.

Usage in Pregnancy: An increased risk of congenital malformations associated with the use of benzodiazepines (diazepam and chlordiazepoxide) has been suggested in several studies. If VERSED is used during pregnancy, apprise the patient of the potential hazard to the

PRECAUTIONS: General: Decrease intravenous doses in elderly and debili-

PRECAUTIONS: General: Decrease intravenous doses in elderly and debilitated patients. These patients will also probably take longer to recover completely after VERSED for induction of anesthesia.

VERSED does not protect against increased intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anesthesia.

Information for patients: Communicate the following information and instructions to the patient when appropriate: 1. Inform your physician about any alcohol consumption and medicine you are now taking, including nonprescription drugs. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous ingestion of alcohol and benzodiazepines. 2. Inform your physician if you are ingestion of alcohol and benzodiazepines. 2. Inform your physician if you are

VERSED* (midazolam HCI/Roche) INJECTION

pregnant or are planning to become pregnant. 3. Inform your physician if you

are nursing. Drug interactions: The sedative effect of IV VERSED is accentuated by pre-medication, particularly narcotics (e.g., morphine, meperidine, tentanyl) and also secobarbital and Innovar (fentanyl and droperido). Consequently, also secoparbital and innovar (tentanyl and droperidor). Consequently, adjust the dosage according to the type and amount of premedication. A moderate reduction in induction dosage requirements of thiopental (about 15%) has been noted following use of IM VERSED for premedication. IV administration of VERSED decreases the minimum alveolar concentration.

Nacy has been noted following use of the Vender of professional Nacy had administration of VERSED decreases the minimum alveolar concentration (MAC) of halothane required for general anesthesia. This decrease correlates with the dose of VERSED administered.

Although the possibility of minor interactive effects has not been fully studied, VERSED and pancuronium have been used together in patients without noting clinically significant changes in dosage, onset or duration. VERSED does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium, or against the increased intracranial pressure noted following administration of succinylcholine. VERSED does not cause a clinically significant change in dosage, onset or duration of a single intubating dose of succinylcholine.

No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, d-tubocurarine, succinylcholine and nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, dyclonine HCI and Cetacaine) have been observed.

Drug/laboratory test interactions: Midazolam has not been shown to interfere

Indocaine, dycionine HCI and Cetacaine) have been observed.

Drug/laboratory test interactions: Midazolam has not been shown to interfere with clinical laboratory test results.

Carcinogenesis, mutagenesis, impairment of fertility: Midazolam maleate was administered to mice and rats for two years. At the highest dose (80 mg/kg/day) female mice had a marked increase in incidence of hepatic tumors and male remaie mice had a marked increase in increance of nepatic tumors and male rats had a small but significant increase in benigh thyroid follicular cell tumors. These tumors were found after chronic use, whereas human use will ordinarily be of single or several doses.

Midazolam did not have mutagenic activity in tests that were conducted. A reproduction study in rats did not show any impairment of fertility at up to

A reproduction study in fats did not show any impairment or ferminy at up to ten times the human IV dose.

Pregnancy: Teratogenic effects: Pregnancy Category D. See WARNINGS section. Midazolam maleate injectable, at 5 and 10 times the human dose, did not show evidence of teratogenicity in rabbits and rats.

Labor and delivery: Use in obstetrics has not been evaluated. Because midators and delivery to the reproduction of the respectable production of the reproductions.

section. Midazolam maleate injectable, at 5 and 10 times the human dose, did not show evidence of teratogenicity in rabbits and rats. Labor and delivery: Use in obstetrics has not been evaluated. Because midazolam is transterred transplacentally and because other benzodiazepines given in the last weeks of pregnancy have resulted in neonatal CNS depression. VERSED is not recommended for obstetrical use. Nursing mothers: It is not known whether midazolam is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when injectable VERSED is administered to a nursing woman. Pediatric use: Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS: See WARNINGS concerning serious cardiorespiratory events and possible paradoxical reactions. Fluctuations in vital signs following parenteral administration were the most frequently seen findings and included decreased tidal volume and/or respiratory rate decrease (23 3% of patients following IV and 10.8% of patients following IM administration) and apnea (15 4% of patients following IV administration), as well as variations in blood pressure and pulse rate.

Following IM injection: headache (1.3%); local effects at IM site: pain (3.7%), induration (0.5%), rechess (0.5%), muscle stiffness (0.3%). Following IV administration: hiccoughs (3.9%), nausea (2.8%), vomiting (2.6%), coughing (1.3%), "oversedation" (1.6%), headache (1.5%), drowsiness (1.2%); local effects at the IV site: tendemess (5.6%), pain during injection (5.0%), redness (2.6%), induration (1.7%), phlebitis (0.4%). Other effects (1.1%) mainly following IV administration: Respiratory: Laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnea. Cardiovascular: Bigeminy, premature ventricular contractions, vasovagal episode, tachycardia, nodal rhythm. Gastrointestinal: Acid taste, excessive salivation, retching. CNS/Neuromuscular: Retrograde amnesia, euphoria, confusion, a

OVERDOSAGE: Manifestations would resemble those observed with other benzodiazepines (e.g., sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma, untoward effects on vital signs). No specific organ toxicity would be expected.

DOSAGE AND ADMINISTRATION: VERSED is a potent sedative agent which requires slow administration and individualization of dosage. Clinical experience has shown VERSED to be 3 to 4 times as potent per mg as diazepam. BECAUSE SERIOUS AND LIFE-THREATENING CARDIORESPIRATORY ADVERSE EVENTS HAVE BEEN REPORTED, PROVISION FOR MONITORING, DETECTION AND CORRECTION OF THESE REACTIONS MUST BE MADE FOR EVERY PATIENT TO WHOM VERSED INJECTION IS ADMINISTERED, REGARDLESS OF AGE OR HEALTH STATUS. Excess doses or rapid or single bolus intravenous administration may result in respiratory depression and/or arrest. (See WARN-INGS.) Prior to use refer to the DOSAGE AND ADMINISTRATION section in the complete product information.



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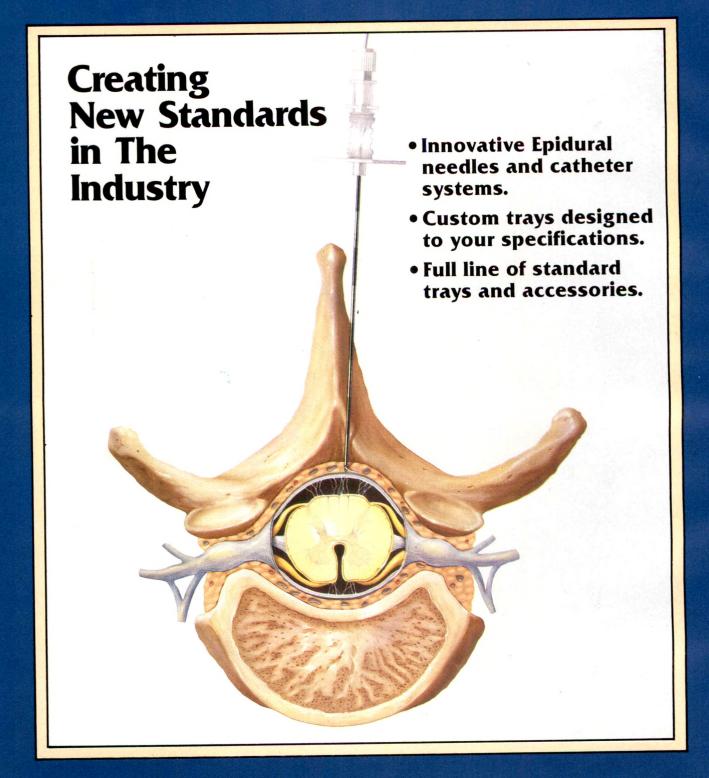
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Isoflurane Partially Preserves Energy Balance in Isolated Hepatocytes During In Vitro Anoxia

Barbara L. Pathak, MD, Gerald L. Becker, MD, Pamela J. Reilly, BS, Kimberly A. Hanson, PhD, MD, and Dennis F. Landers, MD, PhD

PATHAK BL, BECKER GL, REILLY PJ, HANSON KA, LANDERS DF. Isoflurane partially preserves energy balance in isolated hepatocytes during in vitro anoxia. Anesth Analg 1991;72:571–7.

We investigated whether a volatile anesthetic (1.5% isoflurane or 1.0% halothane) or an added anaerobic energy source (10 mM glucose or fructose) could act directly on liver cells to protect energy status during 20–30 min of anoxia. We used hepatocytes freshly isolated from fed rats or rats that had fasted, suspended them in Krebs' buffer, and incubated them in sealed flasks under O_2/CO_2 or N_2/CO_2 (95%:5%). The adenosine triphosphate (ATP) to adenosine diphosphate (ADP) ratio (ATP/ADP) measured cellular energy balance—the balance between overall ATP supply and demand. Lactate levels measured the extent to which ATP was supplied by the nonmitochondrial pathway, (anaerobic) glycolysis.

Maximum values of energy balance were seen in cells from fed rats incubated in the presence of glucose and O_2 . When glucose was replaced by fructose, ATP/ADP decreased and lactate increased. During anoxia (O_2 replaced by N_2), increases in lactate were also seen with glucose; and

ATP/ADP decreased to similarly low values with both substrates. In cells from fasted rats, ATP/ADP decreased significantly below the value for cells from fed rats only in the presence of glucose and O_2 . Compared with cells from fed rats, cells from fasted rats showed decreased lactate in the face of decreased ATP/ADP, suggesting that glycolysis was impaired. Isoflurane partially prevented anoxiainduced decreases in ATP/ADP. This protective effect on energy balance occurred equally with glucose and fructose, but was not seen in cells from fasted rats or with halothane. Thus, 1 MAC isoflurane and some factor(s) related to the fed state combined to protect partially the energy balance in anoxic liver cells through action(s) at the cellular level. The molecular mechanisms of these effects remain to be determined. Further studies will also be needed in more intact systems to determine whether these energy-protective effects of volatile anesthetic and nutritional status influence hepatic preservation under clinically relevant conditions of anoxia and ischemia.

Key Words: ANESTHETICS, volatile—isoflurane. METABOLISM, anaerobic—isoflurane. LIVER, METABOLISM.

The goal of this study was to investigate whether the presence of volatile anesthetic along with added glucose or fructose could protect energy balance in liver cells during anoxia. Intraabdominal surgery, in particular hepatic procedures, exposes the liver to varying degrees of ischemia (1). Ischemia interrupts the supply of metabolic fuels and oxygen (O₂) that generate the energy required to form adenosine triphosphate (ATP) from adenosine diphosphate

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(ADP) in mitochondria. The hydrolysis of ATP to ADP in turn makes energy available to extramito-chondrial reactions essential to liver cell function and viability (Figure 1). Normally, regulatory mechanisms adjust ATP supply to match ATP demand; the resulting steady-state balance between the two processes is reflected in relatively high and constant values of the ATP/ADP ratio. However, because mitochondria provide the bulk of ATP-forming capacity, hepatic anoxia or ischemia causes cellular ATP/ADP to decrease rapidly (2).

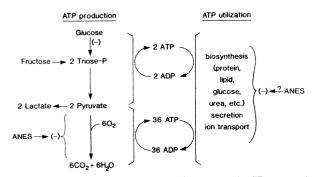
Ischemia-induced hepatic ATP depletion is counteracted to some extent through increased ATP formation via the alternative, O₂-independent pathway of (anaerobic) glycolysis. This pathway forms ATP while converting either endogenous glucose (stored as glycogen) or exogenous glucose or certain other

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<u>Figure 1</u>. Schematic diagram of ATP-forming and ATP-consuming reactions/pathways/processes in hepatic parenchymal cells. (–) indicates inhibition.

simple sugars to lactate. Although glycolysis is greatly activated by decreased ATP/ADP, its relative inefficiency in forming ATP (only 2 ATP per glucose consumed) can sustain ATP/ADP only at considerably lower values than those attained when O₂ is available to support mitochondrial ATP formation. On the other hand, in vitro studies suggest that even the limited ATP formation available through glycolysis may be critical in preventing cell injury and death during anoxia in isolated perfused liver (3) or isolated hepatocytes (4). Fructose appears to be a more effective glycolytic substrate in liver cells than glucose itself. In isolated hepatocytes from fasted rats, which are largely depleted of endogenous glucose reserves (glycogen), exogenous fructose but not exogenous glucose was able to support sufficient ATP formation to maintain cell viability during 2 h of anoxia (3,4). Rates of lactate formation and levels of ATP or ATP/ADP were lower than those in cells from fed rats

Volatile anesthetics also have the potential to affect hepatic ATP levels, although the mechanisms remain incompletely understood. Clinical doses of volatile anesthetics decrease O₂ consumption in liver as well as in other organs (5,6) and directly inhibit O_2 consumption and coupled ATP formation in isolated mitochondria (7). However, the inference that anesthetics must thereby impair hepatic energy balance is contradicted by the normal values of ATP, ATP/ADP, and other measures of high energy phosphate content in cells and tissues exposed to anesthetic doses up to approximately 1.5 MAC under physiologic conditions (8-10). A more detailed consideration of energy metabolism discloses other factors that may offset the inhibitory actions of anesthetics on mitochondrial ATP formation and prevent hepatocellular ATP deficits from developing during anesthetic exposure. First, there are metabolic fuels available in vivo, principally fatty acids, with mitochondrial oxidation

that is not inhibited by anesthetics and that are thus able to support mitochondrial ATP formation (11,12). Second, anesthetics may inhibit ATP-consuming reactions to the same or greater extent as they do ATP-forming ones (Figure 1). The latter situation could account for all of the experimental observations reported from both isolated and intact systems. Oxygen consumption, which is linked only to ATP formation, decreases regardless of whether or not ATP consumption is also inhibited; cellular ATP levels or ATP/ADP, which are determined by the balance between ATP formation and consumption, would not decrease if the latter process were inhibited to at least the same extent as the former by the anesthetic. Known examples of anesthetic inhibition of ATP-consuming reactions include anestheticinduced depressions of cerebral electrical activity and of myocardial contractility (13,14). Because ATP levels or ATP/ADP ratios were found to be well maintained under such conditions (13,15), the associated decrease in O2 consumption (ATP formation) presumably reflected a decrease in ATP supply in homeostatic response to anesthetic inhibition of ATP demand rather than a primary failure of ATP supply due to direct anesthetic inhibition of mitochondrial respiratory chain oxidations.

In fact, it has been proposed that the ability of anesthetics to reduce cellular ATP demand may be energy- and tissue-protective when ATP supply is limited by anoxia or ischemia (16). The experiments with isolated intact hepatocytes described below were undertaken to investigate that possibility: namely, that during O2 deprivation general anesthetics do not exacerbate the ATP/ADP decreases that develop in liver cells and in fact may attenuate those decreases. We also examined the ability of added glucose or fructose (as substrates for glycolysis, the cell's only source of ATP during anoxia) to ameliorate anoxic energy deficits. We also checked the possibility that fasting, by depleting liver cells of endogenous glycolytic substrate, could impair maintenance of cellular energy stores. As stated above, our general goal was to investigate whether exposure of liver cells to volatile anesthetic and/or added glycolytic substrate could help preserve energy balance during anoxia by direct action(s) at the cellular level.

Methods

We used isolated intact hepatocytes in these studies for two reasons. First, we eliminated the possibility that observed effects on hepatocellular energy status might be due to indirect anesthetic action(s) such as a change in blood flow that could affect the supply of O₂ or substrate to liver cells. Second, suspensions of isolated cells, unlike intact liver either in vivo or ex vivo, can be incubated in a precisely defined and homogeneous extracellular environment and accurately sampled for biochemical measurements. The protocol described below was approved by our institution's animal use committee.

Cell Preparation

Adult male Sprague-Dawley rats had free access to water; either they were fed ad libitum or they fasted for 24 h. The rats were anesthetized with 50 mg/kg intraperitoneal pentobarbital and their livers were perfused in situ with Ca2+-free Krebs-Henseleit buffer (pH 7.4) supplemented with 20 mM HEPES, maintained at 37°C, and equilibrated with O₂/carbon dioxide (CO₂) (95%:5%). Establishing the perfusion circuit required cannulation of the inferior vena cava through a right atrial approach, which caused circulatory arrest and death. After 10 min of recirculating perfusion at 30–35 mL/min, the buffer was replaced with 250 mL fresh medium containing 0.4 U/mL type I collagenase (Sigma, St. Louis, Mo.) and the perfusion continued for another 13 min. The swollen, softened liver was then removed from the carcass, immersed in 40-50 mL fresh medium containing added bovine serum albumin (2%), and gently dispersed into small fragments with a glass rod or spatula. The resulting slurry of disaggregated cells was transferred to a 500-mL Erlenmeyer flask and incubated under a flowing O2/CO2 atmosphere in a rotating water bath at 37°C for 15 min to allow damaged cells to lyse. The cell suspension was then filtered through nylon mesh and centrifuged for 1 min at 30 g. The cells were twice more suspended in (fresh) medium and centrifuged. The final pellet diluted to 10-mL final volume contained a total of 2-4 \times 10⁸ cells that were approximately 90% viable by exclusion of trypan blue dye. Cells were stored in plastic tubes on ice and used within 30 min.

Experimental Incubations

In 100-mL round-bottom flasks sitting on ice, 12.5 million cells were suspended to a total volume of 2.0 mL in fresh Krebs-Henseleit buffer (pH 7.4) supplemented with 20 mM HEPES and containing 0.25 mM CaCl₂. Substrates for energy metabolism were added as indicated under Results. The flasks were sealed with rubber caps, through which were

inserted 18-gauge needles for inflow and outflow of gas mixture. An anesthesia machine was used to convey the basic gas mixture (95% O₂ or nitrogen $(N_2)/5\%$ CO₂) from cylinders to the flasks at a designated flow rate (usually 0.5 L·min⁻¹·flask⁻¹), while the desired volatile anesthetic agent was added to the gas mixture by means of a copper kettle vaporizer. Anesthetic concentrations delivered to the flasks were checked by gas chromatography. Incubations were initiated as quickly as possible by turning on the gas flow and transferring each flask from the ice bucket into a 37°C water bath in which the cells were kept suspended by swirling the flasks at 30 rpm. The gas mixture provided was O₂/CO₂ to all flasks for 10 min, followed by 30 min of either O_2/CO_2 or N₂/CO₂, with or without anesthetic as noted under Results. Incubations were terminated by transferring the flasks back into the ice bucket, quickly withdrawing the needles, removing the rubber cap, and pipetting 0.5 mL of 0.2 M perchloric acid forcefully into the cell suspension so that virtually instantaneous quenching occurred. After removal of precipitated membrane and protein by centrifugation, the clear supernatant was adjusted to pH 7.0 with 2 M potassium hydroxide and cooled in ice to precipitate excess potassium perchlorate. The clear supernatant was decanted and stored at -20° C.

Metabolite Determinations

Each sample was thawed, mixed, and passed through a syringe filter (nylon, 0.4μ m mesh, MSI, Westboro, Mass.). Adenosine triphosphate and ADP were determined by a single high-performance liquid chromatography run on a 150 × 3-mm column packed with C_{18} reversed-phase silica, 4- μ m particle size (Nova-Pak No. 86344, Waters, Milford, Mass.). Isocratic elution was carried out at a flow rate of 0.6 mL/min using a mobile phase consisting of 100 mM sodium phosphate buffer (pH 6.0) to which was added 8 mM tetrabutylammonium hydrogen sulfate (Sigma) and 10% (vol/vol) acetonitrile. External standards were used for identification and quantitation of ATP and ADP. Lactate was determined on the same filtered samples by the standard assay using lactate dehydrogenase with spectrophotometric detection of NADH at 339 nm (17).

Data Analysis and Presentation

For each sample, the ratio of ATP to ADP values (ATP/ADP) was calculated and used as the indicator

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Table 1. Energy Status in Hepatocytes Isolated From Fed Rats and Exposed to Isoflurane and/or Anoxia and Glycolytic Substrate In Vitro

	O ₂			N_2
	Glucose	Fructose	Glucose	Fructose
ATP/ADP		**************************************		
-Isoflurane	4.9 ± 0.4	3.0 ± 0.4^{a}	0.9 ± 0.2^{b}	0.9 ± 0.1^{b}
+Isoflurane	5.2 ± 0.4	3.0 ± 0.2^{a}	1.8 ± 0.5^{b}	$1.8 \pm 0.4^{b,c}$
Lactate (µmol/10 ⁷ cells)				
-Isoflurane	2.3 ± 0.4	6.1 ± 0.3^{a}	4.2 ± 0.3^{b}	7.4 ± 0.7^{a}
+Isoflurane	3.1 ± 0.5	$5.8 \pm 0.6^{\circ}$	4.3 ± 0.5	6.0 ± 0.4^a

Values are expressed as mean \pm sem; n = 10.

O2, oxygen; N2, nitrogen; ATP/ADP, ratio of adenosine triphosphate to adenosine diphosphate.

 $^{\circ}P \le 0.05$ compared with – isoflurane category

of cellular energy balance. For short-term anoxic exposure such as that used in this study, the ATP/ ADP ratio is thought to reflect more sensitively the cellular energy status—fundamentally the dynamic balance between ATP formation and consumptionthan either ATP concentration alone or more complex expressions such as energy charge (8,18). Lactate concentration was used as a measure of glycolytic ATP formation, which normally increases as mitochondrial ATP formation is inhibited. The dependence of ATP/ADP and lactate on each of the four independent variables—feeding status, glycolytic substrate, oxygen level, and anesthetic level-was determined by analysis of variance with repeated measures on the last three variables, as all combinations of those variables were examined in every hepatocyte preparation. Post hoc comparisons between pairs of groups were performed with paired or unpaired *t*-test, as appropriate. P < 0.05 was considered to be statistically significant.

Results

In cells from fed rats (Table 1) incubated under O₂ in the absence of anesthetic, ATP/ADP was lower with fructose than with glucose (3.0 vs 4.9), and lactate levels were higher (6.1 vs 2.3). The ATP/ADP ratio was significantly decreased under N₂ compared to O_2 , reaching the same low value with both substrates (0.9). Activation of glycolysis for ATP formation under N₂ was confirmed by the increased lactate level seen with glucose in going from O_2 to N_2 (2.3 vs 4.2); lactate with fructose did not increase under N_2 (6.1 vs 7.4) but may have already been near-maximal under

As to the effect of anesthetic, ATP/ADP under O₂ was the same in the presence and absence of isoflu-

rane with both glucose (5.2 vs 4.9) and fructose (3.0 vs 3.0). In contrast, ATP/ADP under N2 was significantly higher in the presence compared with the absence of isoflurane (1.8 vs 0.9) with added fructose; although the identical mean ATP/ADP values were obtained with glucose, the larger standard errors kept P > 0.05. These anesthetic-related effects on ATP/ ADP under N2 were not accompanied by significant differences in lactate (4.3 vs 4.2 with glucose; 6.0 vs 7.4 for fructose).

In cells from fasted rats (Table 2) incubated under O₂ without anesthetic, ATP/ADP with glucose was significantly lower than it had been in cells from fed rats (2.6 vs 4.9), whereas ATP/ADP with fructose was the same in fasted and fed cells (2.9 vs 3.0). Glucose was thus less effective in fasted than in fed cells and in fact was no better than fructose in maintaining ATP/ADP (2.6 vs 2.9) under O_2 . Despite decreased ATP/ADP in fasted cells incubated with glucose under O_2 , compensatory glycolytic activity was absent: lactate levels remained lower than with fructose (1.4 vs 3.1). In going from O_2 to N_2 , ATP/ADP values decreased significantly with both substrates; again, lactate levels did not increase with either glucose or fructose. In contrast to the cells from fed rats, ATP/ ADP under N₂ was slightly higher with fructose compared to glucose (0.6 vs 0.4); the difference, although small, was seen consistently in each experiment and thus achieved statistical significance because such comparisons of data obtained within the same experiments were preserved in the repeatedmeasures feature of the data analysis. Finally, in cells from fasted rats, there were no differences attributable to the presence or absence of isoflurane. Specifically, ATP/ADP values under N2 were not higher in the presence than in the absence of isoflurane, in contrast to the finding in cells from fed animals.

Table 3 shows the data from a separate experiment

^a P < 0.05 compared with glucose values in the same (O₂ or N₂) category. ^b P < 0.05 compared with O₂ values in the same (glucose or fructose) category.

<u>Table 2.</u> Energy Status in Hepatocytes Isolated From Fasted Rats and Exposed to Isoflurane and/or Anoxia and Glycolytic Substrate In Vitro

	O_2			N_2
	Glucose	Fructose	Glucose	Fructose
ATP/ADP	The second secon			
-Isoflurane	2.6 ± 0.3^{a}	2.9 ± 0.3	0.4 ± 0.1^{b}	$0.6 \pm 0.1^{b,c}$
+Isoflurane	3.3 ± 0.4^{a} .	3.0 ± 0.3	0.5 ± 0.2^{b}	$0.9 \pm 0.3^{b,c}$
Lactate (µmol/10 ⁷ cells)				
-Isoflurane	1.4 ± 0.3	$3.0 \pm 0.6^{a.c}$	1.7 ± 0.1^a	$3.3 \pm 0.6^{a.c}$
+Isoflurane	2.0 ± 0.5	$3.8 \pm 0.4^{a.c}$	2.5 ± 0.6	3.3 ± 0.6^a

Values are expressed as mean \pm sem; n = 10. Abbreviations as in Table 1.

Table 3. Energy Status in Isolated Hepatocytes Exposed to Isoflurane or Halothane and/or Anoxia in Vitro

	Isoflurane		Halo	thane
	O_2	N_2	O_2	N ₂
ATP/ADP				THE PARTY OF THE P
-Anesthetic	5.8 ± 0.7	$0.8 \pm 0.1^{\circ}$	7.4 ± 1.1	1.2 ± 0.1^{a}
+Anesthetic	4.5 ± 0.4	$1.1 \pm 0.1^{a,b}$	7.3 ± 0.9	1.2 ± 0.2^a
Lactate (μ mol/10 ⁷ cells)				
-Anesthetic	4.0 ± 0.5	6.5 ± 1.3^{a}	2.7 ± 1.1	5.6 ± 0.1^{a}
+Anesthetic	5.1 ± 0.8	7.9 ± 2.1^{a}	2.8 ± 0.6	6.2 ± 1.0^{a}

Values are expressed as mean \pm SEM; n=5 for isoflurane, n=8 for halothane. Abbreviations as in Table 1.

carried out solely to compare isoflurane and halothane at approximately 1 MAC for their ability to alter energy status in isolated hepatocytes during in vitro anoxia. In this separate series of incubations, the period of anoxia was 20 min rather than 30 min, only cells from fed animals were used, and 10 mM glucose was the added substrate throughout. Despite a smaller number of replications (n = 5 rather than 10) and a shorter period of anoxic exposure than in the series of Table 1, ATP/ADP values were again higher with 1.4% isoflurane present than in paired control incubations (isoflurane absent) using cells from the same preparation (1.1 vs 0.8). With 1% halothane, no difference at all in ATP/ADP during anoxia was seen with eight other cell preparations, each incubated in the presence and absence of that agent (1.2 vs 1.2).

Discussion

The baseline values and responses of our experimental system confirmed its suitability for addressing the questions posed in this study. Under conditions closest to physiologic—i.e., cells from fed rats, glucose and $\rm O_2$ present, anesthetic absent—ATP/ADP

was at its maximum (\approx 5), in the range of values reported by others (3,18). Replacing O_2 with N_2 reliably produced metabolically significant anoxia, indicated by substantial decreases in ATP/ADP with all combinations of added substrate, feeding status, and anesthetic exposure.

Supplementing exogenous substrate by including 10 mM glucose or fructose in the medium did not prevent substantial decreases in hepatocellular ATP/ ADP from occurring under anaerobic conditions. Values of ATP/ADP obtained under N₂ were the same with glucose and fructose in cells from fed rats, whereas cells from fasted rats showed small but consistent elevation of ATP/ADP with fructose compared to glucose. The ineffectiveness of exogenous glucose in supporting hepatic glycolytic metabolism has been repeatedly documented (3,4; for review see Reference 19). The marginal ability of exogenous fructose to enhance glycolysis during anoxia may be outweighed by the recognized adverse effects of fructose on hepatic energy balance when O2 is present and ATP levels are higher (for review see Reference 20).

Differences related to endogenous substrate levels were also investigated by comparing cells from fed

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 $^{^{}a}$ P < 0.05, fasted vs fed rats (data given in Table 1).

 $^{^{}b}$ P < 0.05 compared with data for similar group (glucose or fructose) with O₂.

 $^{^{\}circ}P \le 0.05$ compared with glucose values in similar group (O₂ or N₂).

 $^{^{}a}P < 0.05$ compared with similar (isoflurane or halothane) values for O_{2} .

 $^{^{\}it b}$ P \leq 0.05 compared with the value (isoflurane, N₂) for –anesthetic.

and fasted animals. Cells from fasted animals, known to be largely depleted of endogenous glucose (glycogen), did not show significantly lower ATP/ADP values after 30 min of anoxia than did cells from fed animals, whether glucose or fructose was the exogenous substrate. This was true despite the fact that cells from fasted rats in general showed lower lactate levels in the face of decreased ATP/ADP than did cells from fed rats, confirming a previous report of impaired glycolytic responses to energy deficits as a result of fasting (4). We conclude that manipulation of glycolytic substrate, changing either the species of exogenous substrate or the amount of endogenous substrate, in itself promises no significant advantage in preserving energy balance in liver cells during short-term anoxic exposure. A similar conclusion was reached by Biebuyck (21).

In contrast, exposure to isoflurane did show significant preservation of hepatocellular energy balance during anoxia: under N_2 , ATP/ADP in cells from fed rats was higher in the presence than in the absence of approximately 1 MAC isoflurane. This protective effect was seen equally with glucose and fructose as with exogenous substrates. The effect was not observed when cells from fasted rather than fed rats were used, nor when an equianesthetic dose of halothane was used in place of isoflurane. As previously reported, neither anesthetic at 1 MAC produced any change in ATP/ADP in isolated hepatocytes in the *absence* of anoxia (i.e., under O_2) (10).

The findings just described raise questions that cannot all be answered from currently available data. First, the experimental system employed is a rather simplified approximation of physiologic conditions in vivo, although widely used and accepted for shortterm in vitro studies of hepatic metabolism (3,4,10,11). The existence of the effects noted here needs to be confirmed in more complex, intact systems. Second, we have not yet determined whether the observed increase in ATP/ADP with isoflurane is associated with protection of hepatic function (the rates of vital ATP-dependent reactions in liver cellssee Figure 1) or of overall cellular viability. Third, because the anesthetic concentration dependence of ATP/ADP effects was not examined, the presence or absence of such effects of either isoflurane or halothane at doses other than 1 MAC cannot be inferred from the data of this study and remains to be investigated.

As to the metabolic basis of the protective effect of 1 MAC isoflurane under N₂, the observed increase in ATP/ADP could have resulted from any combination of changes in ATP supply and/or demand that increased the former relative to the latter. The data of

this study *do* shed some light on this question, in that an anesthetic-induced change in ATP supply can be ruled out. Lactate values were not different in the presence and absence of isoflurane; therefore glycolytic ATP formation was not changed. Furthermore, any change in mitochondrial ATP formation was precluded because this process is completely shut down in the absence of O2. This leaves only the possibility that isoflurane protected ATP/ADP under N₂ solely by decreasing ATP demand—i.e., by lowering the rate(s) of one or more ATP-utilizing reactions. We are currently attempting to measure directly the rates of overall ATP consumption in isolated hepatocytes to confirm the predicted inhibitory effect of isoflurane (and the absence of same for halothane) and to identify the specific ATPconsuming reaction(s) affected. The fact that isoflurane failed to protect energy balance (increase ATP/ ADP) during anoxia when cells from fasted rats were used may indicate that the major ATP-consuming reaction(s) inhibited by isoflurane is diminished in the fasted state. Among the principal reactions in this category would be those of protein or lipid biosynthesis.

The present study appears to be the first to demonstrate that 1 MAC isoflurane actually helps preserve liver cell energy balance during anoxia (whereas 1 MAC halothane has no such effect). The demonstration of this protective effect may have been crucially dependent on the specific experimental conditions used in this study. Relatively short periods of anoxic exposure may have prevented enzymes that catalyze ATP-consuming reactions from being degraded to the extent that inhibition of their activity by isoflurane could not be detected. Also, the use of anoxia (0% O_2) rather than hypoxia may have eliminated vestiges of mitochondrial ATP formation, anesthetic inhibition of which would have decreased ATP/ADP and thus opposed or even canceled ATP/ ADP increases resulting from anesthetic inhibition of ATP consumption (22).

Our work agrees with other studies reporting that at equianesthetic doses, isoflurane is less detrimental to liver cells than is halothane under conditions of O₂ deprivation in liver. This difference between agents was seen in the viability of cultured hepatocytes during severe hypoxia of longer duration (23) and hepatic function (lactate uptake) during ischemia/reperfusion (24). Results from these other studies, like ours, were consistent with this difference between agents arising from direct action(s) of the anesthetics at the cellular level. The specific chemical interactions between anesthetic molecules and specific cellular

components that could account for such a difference between agents remain to be elucidated.

Because the ability of ischemic liver to maintain or regenerate ATP is strongly related to subsequent tissue viability and function (3,4,25,26), any contribution that anesthetics might make to protecting hepatic energy balance during ischemic or anoxic intraoperative conditions is potentially important. Studies are needed in more intact systems to determine whether the energy-protective effects of volatile anesthetic and nutritional status demonstrated in this study influence hepatic preservation under clinically relevant anoxic or ischemic conditions.

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Rate-Dependent Induction Phenomena With Propofol: Implications for the Relative Potency of Intravenous Anesthetics

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STOKES DN, HUTTON P. Rate-dependent induction phenomena with propofol: Implications for the relative potency of intravenous anesthetics. Anesth Analg 1991;72: 578-83.

To establish anesthesia with minimal respiratory and cardiovascular depression using propofol, the effects of varying the rate of delivery on anesthetic induction dose requirements and hemodynamic changes were studied in four groups of 20 patients each undergoing body surface surgery. All patients were premedicated with temazepam and received 1.5 μ g/kg fentanyl 5 min before induction. Propofol was delivered at 50, 100, or 200 mg/min by the Ohmeda 9000 infusion pump (groups 1, 2, and 3, respectively) or by bolus of 2 mg/kg (group 4) until loss of verbal contact. Anesthesia was maintained thereafter with propofol infused at 6 mg·kg⁻¹·h⁻¹. Using slower infusion rates, induction

took significantly longer (124, 92, 62, and 32 s in groups 1, 2, 3, and 4, respectively) and was achieved with significantly smaller doses of propofol (1.40, 1.96, 2.61, and 2.15 mg/kg in groups 1, 2, 3, and 4, respectively). Slow infusion (groups 1 and 2) caused less depression of systolic and diastolic blood pressure than rapid infusion (groups 3 and 4), bu! the differences were not statistically significant. Patients in groups 3 and 4 had significantly greater decreases in pulse rate and a greater incidence of apnea than did patients in group 1. There was no correlation between the size of the induction dose and subsequent maintenance requirements of propofol. The finding that the sleep dose of propofol is reduced at slower infusion rates has important practical and theoretical implications when considering the relative potencies of intravenous anesthetics.

Key Words: ANESTHETICS, INTRAVENOUS—propofol.

Induction of anesthesia with propofol ("Diprivan"; ICI Pharmaceuticals) is associated with significant reductions in systemic arterial blood pressure (1). Doses of 2.0–2.5 mg/kg cause marked vasodilatation and reductions in cardiac output (2,3). Cardiovascular depression is more pronounced in the elderly and is also influenced by the dose and rate of propofol administration. The importance of injecting propofol slowly in order to avoid an overdose and to minimize cardiorespiratory depression is widely accepted (4).

The Ohmeda 9000 syringe pump incorporates a "bolus" facility capable of delivering infusate at 5, 10, or 20 mL/min. This facility was used to investigate the effects of variable rates of propofol administration on induction dose requirements and hemodynamic changes in healthy adults.

Once induced, the maintenance of anesthesia is dependent on achieving and maintaining adequate concentrations of drug in the bloodstream. Although a blood concentration of 3 μ g/mL of propofol is effective in 95% of morphine-premedicated patients (5), accurate prediction of the amount of drug required to achieve comparable blood levels in different patients is extremely difficult (6). It was thought possible that the induction dose in a particular individual might be used to predict the necessary maintenance requirements. To test this hypothesis, a comparison was made between the doses of propofol required to induce and maintain anesthesia in the present study.

Methods

Eighty ASA physical status I and II patients aged 18–55 yr scheduled for body surface surgery under general anesthesia were studied. Hospital Ethical Committee approval was obtained, and all patients participating in the study gave informed consent. Exclusion criteria included serious impairment of major organ function, obesity, suspected pregnancy, or intercurrent medication likely to influence the hemodynamic responses to anesthesia. All patients

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Table 1. Demographic Details

	Group 1	Group 2	Group 3	Group 4
n	19	20	20	20
Sex (M/F)	8/11	5/15	5/15	9/11
Weight (kg)	72.5 ± 9.25	76.3 ± 13.61	75.3 ± 16.57	71.9 ± 13.67
Height (cm)	171.8 ± 8.67	173.3 ± 9.73	173.7 ± 14.02	173.4 ± 12.19
Age (yr)	36.4 ± 11.4	34.8 ± 11.96	34.8 ± 12.75	36.2 ± 10.34

Values for weight, height, and age are expressed as mean \pm sp. There were no statistically significant differences between groups.

were premedicated with 20 mg of oral temazepam approximately 1 h before surgery. On arrival in the anesthetic room, patients were randomly allocated to one of four study groups. All patients then received 1.5 μ g/kg fentanyl administered through an indwelling intravenous cannula 5 min before the commencement of induction. Anesthesia was induced with propofol (10 mg/mL) infused at 5 mL/min (group 1), 10 mL/min (group 2), or 20 mL/min (group 3) until loss of verbal contact with the patient. Patients in group 4 received 2 mg/kg propofol by manual injection over 20 s, and further 20-mg increments were administered at 10-s intervals, if necessary, until loss of verbal contact. Immediately after induction, an infusion of propofol was commenced at 6 mg·kg⁻¹. h⁻¹ in all patients. The infusion rate was adjusted to a level at which movement in response to surgical stimulus was eliminated for the duration of surgery. After induction all patients breathed a mixture of 66% nitrous oxide in oxygen through a face mask attached to a Mapleson A breathing system. Ventilation was assisted in the event of prolonged apnea.

The induction dose of propofol and duration of induction were recorded, and a venous blood sample was collected at the endpoint of induction from the arm opposite to the infusion site. Blood samples were stored at 4°C in potassium oxalate tubes and were subsequently assayed for whole blood propofol concentration using a high-pressure liquid chromatographic technique (ICI Pharmaceuticals) (7). Noninvasive measurements were made of systolic and diastolic arterial pressures (Dinamap; Critikon), pulse rate (electrocardiogram oscilloscope; Simonsen and Weel), and respiratory rate (2540 Volume Meter; Ohmeda). These readings were recorded immediately before injecting fentanyl, 1 min before induction, every minute for 5 min, and then every 5 min thereafter for the duration of surgery. The cumulative volume of propofol infused displayed by the pump was recorded every 5 min. Propofol was discontinued after the completion of surgery, and times to eyeopening upon command, correct recitation of date of birth, and sitting unaided were recorded.

Kruskall–Wallis and χ^2 tests were used to compare demographic data. Paired Student's *t*-test and analysis of variance were used to analyze the statistical significance of changes in arterial pressure, heart rate, and respiratory rate. Induction and maintenance doses, together with induction and recovery times, were compared using the Kruskall–Wallis test and Wilcoxon rank sum test, where indicated. Induction doses of propofol were plotted against maintenance doses, and Spearman correlation coefficients were calculated for each group.

Results

In 80 patients entered into the study, data collection was complete except for one patient in group 1 who was excluded from analysis. There were no differences in age, weight, height, or ASA physical status between patients in the four study groups (Table 1).

The rate of propofol administration had a significant effect on the pattern of induction of anesthesia. As the infusion rate of propofol became slower, there was a significant reduction in induction dose and increase in induction time (P < 0.001; Table 2). Excitation and injection pain were less prominent during slow administration of propofol (group 1), and apnea occurred more commonly at faster rates of administration (groups 3 and 4). Induction by slow infusion was considered to be acceptable by both patients and anesthetists.

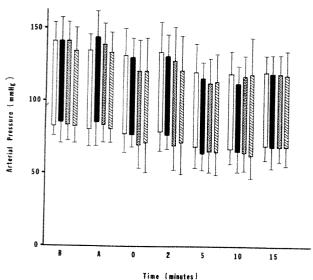
Systolic and diastolic arterial pressures decreased during induction in all groups (Figure 1). Decreases in pressure were less marked at lower infusion rates, but differences within and between groups did not reach statistical significance when subjected to analysis of variance. Further analysis revealed that patients in groups 2–4 were more likely to experience a decrease in systolic arterial pressure of greater than 20% from the postfentanyl baseline than were patients in group 1 (P < 0.02-0.001; χ^2 and Fisher's exact test). Reductions in heart rate occurred in all groups after induction; cardiac slowing was significantly

Table 2. Induction Details

	Group 1	Group 2	Group 3	Group 4
Induction dose (mg/kg)	1.397 ± 0.333^a	1.963 ± 0.371^a	2.609 ± 0.457^a	
Induction time (s)	123.5 ± 28.93^{b}	92.0 ± 19.02^{b}	61.7 ± 14.06^{h}	2.147 ± 0.269^a
Blood propofol (µg/mL)	3.865 ± 2.099	5.373 ± 4.473	5.756 ± 6.301	31.8 ± 10.35^b
Injection pain	0	4	3.750 = 0.501	5.801 ± 7.188
Excitation	0	2	1	4
Apnea (>30 s)	3^c	6	$\frac{1}{13^c}$	1
Quality of induction		U	13	14°
By anesthetist				
Good	16	17	10	4.0
Adequate	3	1	18	18
Poor	0	, ,	2	2
By patient	, ,	2	U	0
Pleasant	19	19	20	
Unpleasant	0	17	20	20
		1	0	0

Values for induction dose, induction time, and blood propofol are expressed as mean \pm sp.

Significantly less patients became apneic in group 1 compared with groups 3 and 4 (P < 0.01).



<u>Figure 1</u>. Influence of induction on arterial pressure. Mean systolic and diastolic arterial pressures (and one standard deviation) during the induction period. B, before fentanyl; A, 1 min before induction; 0, endpoint of induction and 2, 5, 10, and 15 min thereafter. \Box , group 1; \blacksquare , group 2; \boxtimes , group 3; \boxtimes , group 4. No significant differences within or between groups.

greater in groups 3 and 4 than in group 1 5 min after induction (P < 0.043–0.005; Figure 2). Slowing of respiration at induction was most marked in group 3, but again between-group differences were not significant (Figure 3). Significantly more patients experienced apnea of more than 30-s duration after rapid administration of propofol (groups 3 and 4) than after slow infusion (group 1; Table 2).

There was no correlation between propofol induction and maintenance dose requirements during the

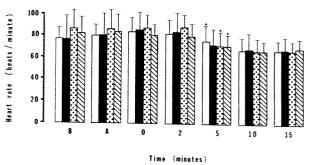


Figure 2. Influence of induction on heart rate. Mean heart rates (and one standard deviation) during the induction period. B, before fentanyl; A, 1 min before induction; 0, endpoint of induction and 2, 5, 10, and 15 min thereafter. \square , group 1; \blacksquare , group 2; \square , group 3; \square , group 4. *Cardiac slowing was greater in groups 3 and 4 compared with group 1 5 min after induction (P < 0.05).

first 30 min of surgery in any of the groups. Maintenance doses did not differ significantly between groups with the exception of a lower requirement in group 2 compared with group 4 during the first 10 min of anesthesia (Figure 4). Blood levels of propofol at the endpoint of induction were extremely variable, and the mean concentrations did not differ between groups (Table 2).

Duration of anesthesia and recovery times were similar in all groups (Table 3). No adverse reactions were encountered to any drugs used in the study.

Discussion

Reductions in systolic blood pressure of more than 25% often occur during induction of anesthesia with

[&]quot;Statistically significant differences (except comparison of group 2 with group 4) (P < 0.001). *Statistically significant difference (all comparisons) (P < 0.001).

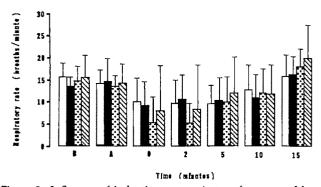


Figure 3. Influence of induction on respiratory frequency. Mean respiratory frequencies (and one standard deviation) during the induction period. *B*, before fentanyl; *A*, 1 min before induction; 0, endpoint of induction and 2, 5, 10, and 15 min thereafter. □, group 1; ■, group 2; □, group 3; ■, group 4. There were no significant between-group differences.

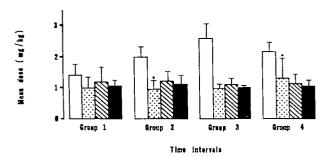


Figure 4. Propofol maintenance infusion requirements. Mean infusion requirements of propofol in mg/kg (plus one standard deviation) for groups 1-4 at time intervals during the maintenance period compared with induction dose. \Box , induction dose; \Box , 0-10 min; \blacksquare , 11-20 min; \blacksquare , 21-30 min. *Requirements during the first 10 min were lower in group 2 compared with group 4 (P < 0.05).

propofol (3,8), an effect more marked in the elderly (9). These studies have concluded that this hypotensive effect can be explained by both separate and combined decreases in the resistance of the vascular bed and the cardiac output. The latter is probably due to a combination of myocardial depression and preload reduction resulting from increased venous capacitance (10,11). Reducing the rate of propofol administration and, therefore, the peak blood concentration might be thought to lessen adverse cardiovascular side effects. Our results suggest that any such alleviation is not dramatic, and there was no significant difference in the blood propofol levels between groups at the end of induction. Reductions in arterial pressure were observed in all groups, but although the decreases were less marked when propofol was infused slowly, the differences between groups did not reach statistical significance using analysis of variance. That decreases in systolic pressure exceeding 20% of the baseline reading were

more common when propofol was administered more rapidly may, however, be of clinical importance.

Cardiac slowing and apnea were more dosedependent than were changes in blood pressure. Rapid infusion rates and bolus injections produced a significantly greater reduction in heart rate than the slowest infusion rate. This effect may be mediated by the action of propofol on baroreceptor activity (12) as the vagotonic effects of fentanyl were the same in each group.

Slow infusion of propofol resulted in a mean induction time greater than 2 min and a decrease in induction dose. No excitatory effects occurred, and all patients considered slow induction to be acceptable. Apnea occurred significantly less frequently during slow infusion (15%) than with either rapid infusion (65%) or bolus (70%) administration. The higher overall incidence of apnea when compared with other studies is probably attributable to the concurrent administration of fentanyl.

The relationships between rate of drug administration, induction time, and dose requirement observed in the present study pose interesting questions that merit further consideration. Differing rates of intravenous drug administration will result in variations in the early stages of drug distribution. Rapid administration leads to an early peak in plasma concentration providing a large gradient for both uptake into the central nervous system (CNS) and for drug redistribution to other tissues. The early establishment of a large gradient for CNS uptake would explain the reduction in induction time with increasing infusion rate and the use of bolus doses (Table 2). Furthermore, the effectiveness of a fixed dose of drug will be dependent on the rate of administration. Rolly et al. (13) failed to induce anesthesia in 10% of unpremedicated patients who received 2 mg/kg propofol injected over 60 s, whereas the same dose was effective in all patients when injected over 5 s. How are we then to explain the findings of the present study, in which slower drug administration resulted in significant reductions in the total dose of propofol required for induction? Also, based on this finding it is difficult to explain how when the infusion rate was very high (as in the bolus dose), the total dose required for induction again decreased (Table 2). These findings call into question current definitions of absolute and relative drug potency.

The slow increase in plasma concentration associated with a slow infusion provides a lower but more sustained gradient for even drug delivery throughout the CNS. If passive concentration gradients were the only determinant of drug transfer into the CNS, then

Table 3. Recovery Times

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	Group 1	Group 2	Group 3	Group 4
Duration of infusion (min) Time (min) from discontinuation of infusion to:	47.3 ± 20.22	41.7 ± 12.65	52.6 ± 20.92	43.4 ± 16.52
Eye opening Reciting date of birth Sitting unaided	7.6 ± 3.10 8.8 ± 4.68 58.5 ± 42.57	8.5 ± 4.63 9.9 ± 5.04 55.6 ± 58.07	8.8 ± 4.83 10.7 ± 5.04 77.8 ± 58.95	8.5 ± 4.82 10.0 ± 5.08 57.6 ± 46.12

Values are expressed as mean ± sp.

There were no statistically significant differences between groups.

the slower the infusion rate, the larger the total dose that would be required to achieve the effective drug concentration. Because this is not so (Table 2), some other explanation is required. The time to onset of drug action depends on both the circulation time and the biophase kinetics (14). Gillies and Lees (15) showed that propofol (2.5 mg/kg) injected over 40 or 80 s resulted in a significantly slower induction than etomidate (0.3 mg/kg) injected at equivalent rates. This suggests that the physicochemical properties of propofol are such that it requires a finite transport time to reach the biophase. If we assume that this "biophase delay" is the rate-limiting process regulating the concentration of propofol at its site of action, then slower infusion rates could easily reach the necessary concentration at the site of action with a lower total dose than the faster infusion rates. This concept implies that higher infusion rates will invariably lead to an overdose of propofol. This is the price of achieving a rapid induction with propofol.

Why, then, was the induction dose after bolus administration (group 4, Table 2) less than that after rapid infusion? Bolus injection rapidly produced a high peak plasma concentration allowing earlier biophase penetration than the faster infusion. Because the initial bolus dose of 2 mg/kg propofol was administered over 20 s, and because 70% of subjects were asleep after a further 10 s, incremental doses were not often needed. By contrast, when the drug was infused, an overshoot in the dose delivered was unavoidable because of the time delay between drug entering the circulation and the endpoint of induction (due to circulation time and the biophase factors described above). This overshoot was most marked with rapid infusion, explaining why patients in this group had the highest induction dose requirements.

The present study has established the induction characteristics of four different induction methods using propofol. Which of the four should be used to compare the relative potency of propofol with other agents? The answer to this question is as yet uncertain but our results would indicate that the rate of administration must be accurately specified when discussing the relative properties of different intravenous induction agents.

Pharmacokinetic modeling allows the prediction of the infusion rates required for the maintenance of effective blood levels of intravenous anesthetics (6). Computer-controlled techniques of administration have been described that can rapidly achieve the required anesthetic blood concentrations without overshoot (16). A simple manual infusion scheme has also been developed based on the computer model (17). The major disadvantage of such models is the inherent interindividual variability in drug-handling between patients (6), resulting in excessive or inadequate blood levels. In the present study, the propofol induction dose was not helpful in predicting maintenance infusion requirements for individual patients. This finding was not unexpected because induction and maintenance dose requirements are influenced by two independent pharmacokinetic parameters namely, initial volume of distribution and clearance, respectively. Maintenance infusion rates were largely equivalent between groups (Figure 4). Maintenance infusions were initiated at a rate of 6 $mg \cdot kg^{-1} \cdot h^{-1}$, and this may have been too high to detect differences in the minimum drug requirements for maintenance. Upward adjustment of maintenance infusion rate was required in only 20% of cases.

In summary, varying the rate of infusion induction of anesthesia with propofol in healthy adults does not result in major differences in changes in arterial pressure. Furthermore, the hypothesis that the propofol induction dose requirement may be used to predict maintenance requirements was not supported by this study. Induction by slow infusion can, however, be recommended because of the reduced dose requirements, the lower incidence of apnea, and good patient acceptance. The present study also highlights some major problems in the definition of equipotency of induction agents and suggests that

greater consideration should be given to their biophase characteristics.

We would like to thank anesthetists and surgeons at the Queen Elizabeth Hospital and Birmingham General Hospital for their cooperation and help during this study; Ian Glen and Sue Hunter for their support and helpful comments; and ICI Pharmaceuticals for supplying propofol and for performing drug assays and statistical analyses.

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Comparison of Changes in Transit Time Ultrasound, Esophageal Doppler, and Thermodilution Cardiac Output After Changes in Preload, Afterload, and Contractility in Pigs

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WONG DH, WATSON T, GORDON I, WESLEY R, TREMPER KK, ZACCARI J, STEMMER P. Comparison of changes in transit time ultrasound, esophageal Doppler, and thermodilution cardiac output after changes in preload, afterload, and contractility in pigs. Anesth Analg 1991;72:584–8.

The purpose of this study was to compare how well changes in cardiac output (CO) measured by esophageal Doppler (Doppler) and thermodilution (TD) followed changes in CO measured by transit time ultrasound (TTU). Simultaneous Doppler, TD, and TTU measurements of CO were made before and after changes in preload, afterload, or contractility in seven piglets. Mean changes in each CO method for each type of change in CO were compared by analysis of variance. Changes in TTU CO, TD CO, and Doppler CO were compared by correlation, linear regression, and bias and precision statistics.

Of 86 TTU changes in CO >10%, Doppler changed the same direction as TTU 59 times, changed in an opposite

direction 6 times, and changed <10% 21 times. Thermodilution changed in the same direction as TTU 72 times, in the opposite direction 4 times, and changed <10% 10 times.

Changes (% Δ) in TTU and TD measurements of CO were not significantly different in any group. Changes in Doppler CO and TTU CO were different for two afterload and contractility groups. Percent changes in Doppler CO had a correlation coefficient (r)=0.74, m=0.72, and bias (mean % Δ Doppler CO – mean % Δ TTU CO) = 6.3 \pm 29.7 with % Δ TTU CO. Percent changes in TD CO had an r=0.90, m=0.92, and bias = 5.7 \pm 19.1 with % Δ TTU CO. Cardiac output measured by Doppler underestimated changes in CO due to changes in preload and contractility and exaggerated changes in CO due to changes in afterload.

Key Words: MEASUREMENT TECHNIQUES, CARDIAC OUTPUT—Doppler ultrasound, transit time ultrasound, thermodilution. HEART, CARDIAC OUTPUT—measurement.

Esophageal Doppler ultrasound (Doppler) can measure aortic blood velocity, which, when integrated during systole and multiplied by the cross-sectional area of the aorta (CSA), results in an estimate of stroke volume. Multiplying this estimate times heart rate yields cardiac output (CO). Esophageal Doppler ultrasound CO measurement has the advantage of providing a continuous measurement of CO while being minimally invasive. But the agreement of absolute measurements of Doppler CO with intermittent measurements of thermodilution (TD) CO is variable (1–5). Although it has been proposed that Doppler CO is suitable for monitoring trend changes in CO (2,6,7), this has not been investi-

gated by comparing discrete changes in CO due to specific interventions.

The purpose of this study was to compare how well changes in TD, Doppler, and CO measurement agree with changes in CO measured by a reference flow measurement method, transit time ultrasound (TTU) (8). We chose TTU because it measures stroke volume on a beat-by-beat basis and can detect all the blood moving in the ascending aorta (8). Transit time ultrasound measurements are independent of vessel diameter (9), and, unlike other ultrasound techniques, TTU is also somewhat independent of insonation angle and movement (8).

Methods

This work was approved by the institutional animal research committee. Anesthesia was induced with ketamine in seven Duroc pigs and maintained with

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<u>Table 1</u>. Changes in Cardiac Output With Three Measurement Methods

	п	%ΔFP ± sd	%ΔTD ± sd	%ΔDoppler ± sp
Group 1 (increased preload)	11	32.4 ± 27.3	38.4 ± 31.9	23.9 ± 39.3
Group 2 (decreased preload)	28	-38.5 ± 20.4	-31.8 ± 20.8	-26.0 ± 23.1
Group 3 (increased afterload)	3	6.7 ± 21.3	1.1 ± 21.3	-30.8 ± 7.1
Group 4 (decreased afterload)	12	8.0 ± 28.9	19.8 ± 26.6	50.1 ± 41.7
Group 5 (increased contractility)	13	42.0 ± 29.3	48.3 ± 33.9	$12.8 \pm 26.3^{a,b}$
Group 6 (decreased contractility)	19	-40.7 ± 21.9	-38.4 ± 16.0	-26.6 ± 24.4

%ΔFP, percent changes in transit time ultrasound (flow probe) cardiac output with intervention; %ΔTD, percent changes in thermodilution cardiac output with intervention.

halothane and nitrous oxide in oxygen. Femoral artery catheters were inserted to measure systemic blood pressure. Pulmonary artery catheters were inserted through the right femoral vein. Thermodilution CO was measured in triplicate using 5 mL of 0°C 5% dextrose in water. Esophageal Doppler ultrasound CO was measured with a 24F continuous wave Doppler probe inserted in the esophagus (L3000, Lawrence Medical Systems, Camarillo, Calif.). Transit time ultrasound CO was measured with a calibrated 16-mm ultrasonic flow probe (Transonic 101D, Ithaca, N.Y.) introduced through a median sternotomy incision and placed around the ascending aortic root.

We independently changed the rate of fluid or drug infusion, blood volume (by controlled hemorrhage), the inspired concentration of halothane, positive end-expiratory pressure (PEEP), and inferior vena cava (IVC) compression until the TTU CO changed >10%. Intravenous fluid administration (mean 20 mL/kg) and reinfusion of shed blood were used to increase preload. Controlled hemorrhage (up to 30%-40% of estimated blood volume, in 10% increments), PEEP application, and IVC compression were used to decrease preload. Neosynephrine and nitroprusside infusions were used to increase and decrease afterload, respectively. Dobutamine infusions were used to increase contractility. Increased inspired concentrations of halothane up to 3% and sodium thiopental were used to decrease contractility.

We simultaneously measured TD, Doppler, and TTU CO in triplicate before and after each intervention. The percent change in TD ($\%\Delta$ TD), Doppler ($\%\Delta$ Doppler) and TTU ($\%\Delta$ TTU) CO was calculated for each intervention. When $\%\Delta$ TD and $\%\Delta$ Doppler CO changed >10% in the same direction as the TTU CO change, we considered that TD and Doppler, respectively, had agreed with TTU.

Cardiac output measurements were made until three consecutive TD CO measurements were within 10% of each other, except in the presence of graded hemorrhage or IVC compression. During graded hemorrhage, the preintervention triplicate values were used as the baseline for low (10%–12%), medium (20%–30%), and high (30%–40%) hemorrhage. During IVC compression, changes in perfusion were almost fatal, and it was necessary to release the IVC compression before TD CO could be measured three times. Therefore, IVC compression was done intermittently three times in each pig studied.

Statistics

We used one-way analysis of variance with confirmation by paired t-tests with Bonferroni correction to compare changes in CO and the absolute percent difference ($\%\Delta-\%\Delta$) between the different CO methods. We considered a P<0.05 as statistically significant. We used the coefficient of variance to compare the reproducibility of TD, Doppler, and TTU CO. We used correlation coefficient, regression analysis, and bias and precision to compare the agreement and degree of association of $\%\Delta$ Doppler and $\%\Delta$ TD with $\%\Delta$ TTU and each other. We calculated the sensitivity of both TD and Doppler for detecting changes in TTU CO.

Results

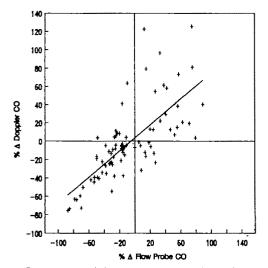
The percent change in CO with all three methods is summarized in Table 1. There was no statistically significant difference between changes in TTU CO and TD CO in any group. In contrast, changes in Doppler CO were different from TTU CO in the decreased afterload and increased contractility groups. The differences in Doppler and TD with TTU are compared in Table 2. The Doppler CO results were similar to the TD CO results only for changes in CO due to increased and decreased preload. Of 95

 $^{^{\}circ}P < 0.05$ in comparison with % Δ FP. $^{\circ}P < 0.02$ in comparison with % Δ TD.

Table 2. Comparison of Differences in Cardiac Output

	n	$(\%\Delta TD - \%\Delta FP) \pm sd$	$(\%\Delta Doppler - \%\Delta FP) \pm sd$	P
Group 1	11	5.9 ± 19.6	8.5 ± 28.8	0.184
Group 2	28	6.7 ± 17.3	12.5 ± 14.3	0.179
Group 3	3	5.6 ± 0.5	37.5 ± 14.3	0.018
Group 4	12	11.8 ± 12.4	42.1 ± 31.5	0.005
Group 5	13	6.2 ± 30.1	-29.2 ± 22.1	0.002
Group 6	19	2.3 ± 17.8	14.1 ± 10.7	0.019
All groups	86	5.7 ± 19.1	6.3 ± 29.7	0.910

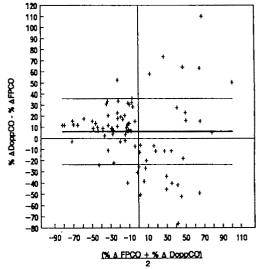
Abbreviations as in Table 1.



<u>Figure 1</u>. Comparison of changes in Doppler CO and transit time ultrasound CO (flow probe).

measurement sets, TTU CO changed >10% 86 times. Of these 86 interventions, Doppler agreed with TTU 59 times, disagreed 6 times, changed <10% 21 times, and had a 62% sensitivity in detecting a 10% change in TTU CO. Thermodilution agreed with TTU 72 times, disagreed 4 times, changed <10% 10 times, and had a 79% sensitivity in detecting a 10% change in TTU CO. The coefficient of variance was 4% \pm 10%, 11% \pm 16%, and 6% \pm 12% for TTU, TD, and Doppler CO, respectively.

The percent change in Doppler CO had a correlation coefficient (r) = 0.74, m = 0.72, and bias (mean % Δ Doppler CO — mean % Δ TTU CO) = 6.3% \pm 29.7% with % Δ TTU CO. The individual data comparing % Δ Doppler CO and % Δ TTU CO are displayed in Figures 1 and 2. The percent change in TD CO had a correlation coefficient (r) = 0.90, m = 0.92, and bias (mean % Δ TTU CO — mean % Δ TTU CO) = 5.7 \pm 19.1 with % Δ TTU CO. The individual data comparing % Δ TD CO and % Δ TTU CO are displayed in Figures 3 and 4. The percent change in Doppler CO had a correlation coefficient (r) = 0.69, m = 0.65, and bias

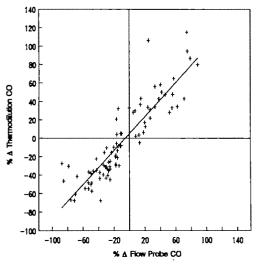


<u>Figure 2</u>. Comparison of changes in Doppler CO (Dopp) and transit time ultrasound CO (flow probe; FP), bias and precision plot. $\%\Delta D$ oppCO $-\%\Delta FPCO = 6.3 \pm 29.7$. Thick horizontal line is mean bias value; thinner lines are \pm sp.

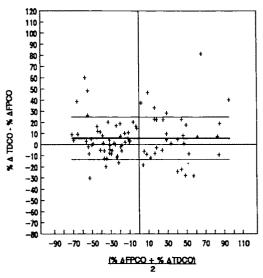
(mean % Δ Doppler CO — mean % Δ TD CO) = 0.4% \pm 32.5% with % Δ TD.

Discussion

Data regarding the accuracy of using Doppler CO to monitor trend changes in CO are conflicting. Esophageal Doppler CO was initially proposed to be useful in monitoring trend changes in CO because most CO Doppler measurement errors were attributed to calibration errors made when measuring the aortic diameter and suprasternal Doppler aortic velocity (2). The authors reasoned that if Doppler CO were inaccurately calibrated, changes in Doppler CO could still be proportional to changes in actual CO. Other authors also concluded that Doppler CO could be used to monitor trend changes in CO (6,7). However, some authors have questioned the usefulness of using Doppler CO to monitor trend changes in CO



<u>Figure 3</u>. Comparison of changes in thermodilution CO and transit time ultrasound CO (flow probe).



<u>Figure 4</u>. Comparison of changes in thermodilution CO (TD) and transit time ultrasound CO (flow probe; FP), bias and precision plot. $\%\Delta TDCO - \%\Delta FPCO = 5.7 \pm 19.1$. Thick horizontal line is mean bias value; thinner lines are \pm sp.

(10), and a recent report concluded that Doppler CO did not monitor trend changes in CO consistently during hemorrhage (11).

Two types of trend monitoring are possible, quantitative and qualitative. One makes use of a device that quantitatively monitors trend changes in CO proportionately with the reference method even though any single measurement might not agree well with the reference method (e.g., a new method whose measurements are always a fixed offset or proportion from the corresponding reference measurements). Comparison of actual values of a quantitative trend monitoring method with a reference

method ideally would show a low (i.e., approaching zero) standard deviation of the bias (precision) with a variable bias value. (An ideal measurement technique would have these statistical results: m = 1, r = 1, b =0, bias = 0, and precision = 0.) Changes in CO measured by an ideal quantitative trend monitoring method, when compared to changes in CO measured by a reference method, would ideally have all data points fall along a line parallel to the line of identity (i.e., r = 1, b = 0, and m = 1) and a horizontal bias and precision plot with no scatter. Devices that quantitatively monitor trend changes in CO well could be readily "recalibrated" by adjusting for the deviation of the bias or m from the ideal. The high %ΔDoppler CO precision values show that Doppler CO did not quantitatively monitor trends in TTU CO well.

A device that qualitatively monitors trends in CO merely changes in the same direction as the reference method. Plots of actual values of a qualitative method with a reference could have regression, correlation, and bias statistics far from ideal. Plots of changes in Doppler CO compared with a reference would ideally show r = 1.

Sensitivity also evaluates the ability to detect qualitative changes. As a diagnostic test, Doppler CO was less sensitive than TD CO in detecting changes in TTU CO that were $\geq 10\%$; Doppler CO sensitivity = 62% and TD CO sensitivity = 79%. Of 59 times when Doppler CO changed $\geq 10\%$, TTU CO had similarly changed 53 (91%) times. Because we titrated our interventions until TTU CO changed $\geq 10\%$ we did not have many false-positive data sets and could not calculate specificity statistics.

It is most interesting that Doppler CO changed >10% in an opposite direction to the reference method six times (7%; increased preload [once], increased afterload [once], decreased afterload [once], increased contractility [twice], and decreased contractility [once]). This contradiction has also been noted by others (6,11). These artifactual changes could lead to inappropriate treatment. It should also be noted that TD also changed in a direction opposite TTU CO in 4 of 86 (5%) interventions.

The most likely source of error in Doppler CO measurement is CSA. Doppler CO actually only measures aortic blood velocity and estimates CSA from an unvalidated nomogram. If the Doppler device accurately measures the patient's actual aortic blood velocity, but the nomogram CSA is different from the patient's actual CSA, then single Doppler CO measurements might be inaccurate but the device should monitor quantitative changes in CO. It should also be possible to "recalibrate" the device to display

Doppler CO accurately. Clinicians who use Doppler CO in this manner, however, must also assume that the CSA doesn't change.

Aortic diameter and CSA change, however, with different interventions, and this may explain why Doppler CO does not monitor quantitative changes in CO well. Decreases in preload decrease CSA (12), and CSA inversely changes with changes in mean arterial pressure and thus probably afterload (3). Cross-sectional area of the aorta may also change inconsistently; it initially decreases and then increases with increased contractility (12). A noncompliant aorta, i.e., a more constant CSA, may also explain why Doppler CO seems to work better in patients with severe aortic atherosclerotic disease than in a control group (13).

Paradoxical increases in Doppler CO seen with hemorrhage (11) might be explained by a decreased CSA with a reflex increase in myocardial contractility leading to increased aortic blood velocity (14). During hemorrhage, the combination of a real (but not measured) decrease in CSA, coupled with a real increase in aortic blood velocity, would be erroneously calculated and reported as an increased Doppler CO.

Compared to both TTU CO and TD CO, Doppler CO underestimates changes in preload and contractility, although the direction of change is often the same. Doppler CO also exaggerates changes in CO due to changes in afterload compared to both TTU CO and TD CO. Although not quantitatively accurate, this feature could be advantageous if clinicians particularly want to detect acute changes in afterload caused by allergic reactions (15), neosynephrine boluses (16), or other events.

Compared to TD CO, Doppler CO appears to have some advantages in addition to being less invasive. Thermodilution could not measure transient changes in CO caused by bolus doses of nitroprusside that changed both TTU and esophageal Doppler. Doppler and TTU could measure lower absolute CO values than TD. Thermodilution was more variable than either TTU or Doppler, with the largest coefficient of variance.

Devices used as trend monitors should also have other characteristics not required of intermittent measurement devices. They should be continuous, or at least provide frequent automatic measurement, and have the capability to store and display trends.

In piglets, Doppler CO did not quantitatively monitor changes in TTU CO. Changes in Doppler CO >10% reflected true changes in CO 59 of 86 (68%) times; however, in 6 of 86 (7%) times, the changes were in the opposite direction to the actual CO change. As a diagnostic test, Doppler CO was less

sensitive than TD CO. Doppler CO underestimated changes in CO due to changes in preload and contractility and exaggerated changes in CO due to changes in afterload.

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Intratracheal Surfactant Administration Restores Gas Exchange in Experimental Adult Respiratory Distress Syndrome Associated With Viral Pneumonia

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The effect of intratracheal surfactant administration was studied in rats with adult respiratory distress syndrome associated with infection with nebulized Sendai virus. Thirty-six hours after infection, animals (n = 7) showed severely impaired gas exchange and acidosis during artificial ventilation (PaO₂ = 152.2 \pm 18.7, PaCO₂ = 65.3 \pm 19.2, pH = 7.26 \pm 0.11) with a pressure-controlled mode, standard frequency of 35/min, peak airway pressure of 15 cm H_2O (15/0), inspiratory/expiratory ratio of 1:2, and FiO₂ = 1. Gas exchange improved (P = 0.02) with

increased ventilator pressures with PEEP (25/4). Forty-eight hours after infection, blood gas tensions could no longer be significantly improved by these same ventilator settings (PaO₂ = 123.8 \pm 31.0, PaCO₂ = 95.1 \pm 43.6, pH = 7.12 \pm 0.16, n = 9). At this time, surfactant replacement dramatically increased arterial oxygenation within 5 min (PaO₂ = 389.4 \pm 79.9) and resulted in a fourfold increase in PaO₂ within 2 h. It is concluded that intratracheal surfactant administration is a promising approach in the treatment of respiratory failure during adult respiratory distress syndrome associated with viral pneumonia.

Key Words: LUNG, ADULT RESPIRATORY DISTRESS SYNDROME—SURFACTANT.

First conceptualized in the late 1960s (1), the adult respiratory distress syndrome (ARDS) is now recognized as the result of lung damage from a number of causes (2), including sepsis, polytrauma, aspiration, multiple organ failure, burns, pneumonia, and many other conditions (3). Although there is no agreement on criteria for the diagnosis of ARDS, an operational definition of ARDS includes at least the following features: an appropriate risk factor; severe hypoxemia refractory to increased inspiratory oxygen concentrations (Pao₂/Fio₂ < 150 mm Hg); decreased lung compliance; bilateral diffuse infiltration on the chest radiograph; and

severe pulmonary edema. At present, despite increased sophistication in methods of respiratory support, mortality associated with ARDS is still around 50%–70% whatever the criteria of diagnosis (4–6).

Development of respiratory failure in ARDS patients is highly correlated with surfactant abnormalities, and the progressive time-course suggests that compositional changes of alveolar phospholipid in ARDS reflect type II cell injury in the course of posttraumatic pulmonary insufficiency (7,8). Furthermore, decreases in surfactant content are found in lung specimens from ARDS patients, and abnormalities in lung elastic properties and increased surface tension of alveolar surfactant are present in postmortem bronchoalveolar lavage fluid (1,9–11).

Clinical trials (12,13) and data from experimental studies indicate that exogenous surfactant therapy can restore lung function in ARDS of different etiology (for reviews, see References 14 and 15). Therefore, although surfactant deficiency does not appear

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to be the primary pathogenic factor in ARDS, surfactant substitution may be a promising approach in the treatment of ARDS (12,13).

Because ARDS is often associated with pneumonia of different etiology, experimental models are required to investigate surfactant replacement therapy in this type of respiratory failure. There are indications that surfactant deficiency plays a role in the development of respiratory failure due to viral pulmonary infection (16,17). These findings are supported by data obtained from mice with influenza A pneumonia that demonstrate positive therapeutic effects of surfactant replacement on lung mechanics (18). No other information is available, to our knowledge, concerning the therapeutic effects of surfactant substitution during respiratory failure caused by viral pneumonia. Therefore, we recently developed a rat model of acute respiratory failure, closely resembling ARDS, caused by infection with Sendai virus (19).

We report the effects of exogenous surfactant therapy and artificial ventilation at different ventilator pressures on arterial blood gas tensions during respiratory failure.

Materials and Methods

Male Sprague–Dawley rats (n = 41, 180–200 g, specific pathogen-free) housed under filter bonnets, with autoclaved food and water available ad libitum, were used. Approval was obtained from the institutional animal investigation committee. Infected animals were removed and kept in a separate facility under identical conditions. Sendai virus (Myxovirus parainfluenza type 1) was propagated in 11-day embryonated chicken eggs. The stock solution thus prepared had a hemagglutination titer of approximately 1:3000.

For inoculation, nonanesthetized animals were exposed for 90 min in an aerosol chamber through which an aerosol (1:2 dilution of stock solution) with a flow of 5 L/min was led. Aerosol was produced with an air jet nebulizer (Ultravent, Malinckrodt Diagnostica, Petten, The Netherlands). This device produces small particles, 0.6–2 μ m in diameter (20), which allows for alveolar deposition of the aerosol (21).

For measurement of arterial blood gas tensions, animals were anesthetized (pentobarbital, 60 mg/kg IP), tracheotomized, and had a metal cannula inserted into the trachea. A catheter (0.8-mm outer diameter) was inserted into the right carotid artery for drawing arterial blood samples. Animals were paralyzed (pancuronium bromide, 0.1 mg/kg IM) and mechanically ventilated (Siemens Servo Ventilator

900C, Siemens Elema, Solna, Sweden) in a pressure-controlled mode, standard frequency of 35/min, peak airway pressure (P_{peak}) of 15 cm H_2O (15/0), inspiratory/expiratory ratio (I/E ratio) of 1:2, and 100% oxygen ($F_{102} = 1$). These ventilator settings result in slight hyperventilation with moderate respiratory alkalosis in healthy Sprague–Dawley rats (19).

To assess the severity of respiratory failure, blood gas tensions were also measured at higher ventilatory airway pressures at different times after infection. $P_{\rm peak}$ was first increased to 20 cm H_2O (20/0), then to 25 cm H_2O with a positive end-expiratory pressure (PEEP) of 4 cm H_2O (25/4). At each ventilator setting 15 min was allowed for stabilization before a 0.3-mL arterial blood sample was collected for measurement of blood gas tensions (ABL 330, Radiometer, Copenhagen, Denmark).

Treatment with surfactant or saline (decided by prior randomization) was performed only in animals with arterial oxygen tension (Pao₂) below 150 mm Hg ventilated at 15/0 and in which increased ventilatory airway pressures (25/4) did not increase Pao₂ above 175 mm Hg.

The effect of surfactant substitution with a natural bovine surfactant, extracted in basically the same way as described by others (22), was evaluated 48 h after infection; 22 animals met the preset criteria for treatment. After randomization, nine animals were treated with 1.5 mL of surfactant (200 mg phospholipids/kg body wt) intratracheally, whereas seven control animals received 1.5 mL of saline intratracheally and six other control animals received no treatment whatsoever except for continuation of the same ventilatory support that was used in the treated animals (25/4). After treatment, ventilator settings remained unchanged and blood gas tensions were monitored for 2 h.

After the experiment, the chest of each animal was opened and a cannula was inserted into the pulmonary artery. The lungs were inflated with a pressure of 20 cm $\rm H_2O$ and maintained at this pressure while being perfused with formalin (4%) through the pulmonary artery. After perfusion, the lungs were removed and kept in formalin (10%) for at least 48 h. Paraffin sections from the right middle lobe were then stained with hematoxylin and eosin and examined microscopically.

All variables were analyzed by the Mann–Whitney U test for between-group comparisons or the Wilcoxon signed rank test for within-group comparisons. All tests of statistical significance were two-tailed, and data were tested at the 0.05 significance level. All data are presented as mean ± standard deviation.

Table 1. Blood Gas Tensions and Acid-Base Stains

	15/0	20/0	25/4
Po ₂ (mm Hg) Pco ₂ (mm Hg)	152.2 ± 18.7 65.3 ± 19.2	162.1 ± 50.7 60.5 ± 14.3	456.5 ± 65.6° 46.8 ± 8.2
pH	7.26 ± 0.11	7.27 ± 0.08	7.35 ± 0.08

Values (expressed as mean \pm sD) are given for seven animals after infection with a lethal dose of Sendai virus, during artificial ventilation. Animals were mechanically ventilated with a Siemens 900C ventilator, in a pressure-controlled mode, at a rate of 35/min, I/E ratio of 1:2, and Fro₂ = 1. Different ventilator pressures were applied: P_{peak} = 15 cm H₂O (15/0), P_{peak} = 20 cm H₂O (20/0), or P_{peak} = 25 cm H₂O with PEEP = 4 cm H₂O (25/4). $^{4}P < 0.05$ compared with 15/0 group.

Results

At 36 h after infection (Table 1), during artificial ventilation (15/0), animals already showed severe signs of respiratory insufficiency with reduced Pao₂, increased arterial carbon dioxide tension (Paco₂), and acidosis. Increasing the ventilatory airway pressures to 20/0 did not significantly change arterial blood gases; further increase of peak airway pressure and introduction of PEEP (25/4), however, almost completely restored arterial blood gas tensions to normal values.

At this stage during the course of the infection, criteria for treatment were not met and therefore surfactant was not injected. Twelve hours later (48 h after infection), six animals had died spontaneously and five animals died during ventilation at 15/0. Therefore, immediately after tracheotomy, higher airway pressures were applied but reduced Pao₂ (101.8 \pm 20.7 [20/0, n = 22] and 123.7 \pm 34.1 [25/4, n = 22], respectively) persisted. These animals were then randomly assigned to three groups. Before treatment there existed no significant differences in Pao₂, Paco₂, arterial pH, and arterial bicarbonate concentrations (HCO₃⁻) between these groups (Table 2).

Five minutes after surfactant instillation, Pao₂ and pH had already significantly increased (Figure 1), whereas Paco₂ decreased significantly below pretreatment values. During the entire observation period, Pao₂ in the surfactant-treated group was significantly higher than in the saline-treated group and in untreated controls. At the end of the observation period (2 h after treatment) Pao₂ in the surfactant-treated group had increased fourfold compared with pretreatment values. Pao₂ values in the saline-treated group and the untreated control groups increased slightly during the 2-h ventilation period. These increases, however, were not statistically significant.

In the surfactant-treated group and in both control groups, Paco₂ decreased and pH concurrently increased during the observation period, whereas Paco₂ reached physiologic values in the surfactant-

treated group only and pH did not reach normal values (Table 2). There were no significant differences in Paco₂ or pH between the surfactant-treated group and control groups.

Histologic examination of rat lungs infected with Sendai virus (Figure 2A) showed swelling of the alveolar walls and alveolar edema containing inflammatory cells. Furthermore, swelling of bronchial epithelial cells and atelectatic areas were present. Examination of lungs of infected animals 2 h after surfactant administration showed clearly improved lung aeration compared with the saline-treated group and untreated controls (Figure 2B and 2C).

Discussion

One of the main functions of the alveolar surfactant system is prevention of end-expiratory collapse of alveoli and small airways (23,24). Furthermore, the surfactant system is essential for balancing lung water content. Pulmonary injury that impairs surfactant production or disturbance of the arrangement of phospholipids and surfactant-associated proteins in the alveolar lining, may, therefore, result in pulmonary edema. Clements predicted in the early 1960s that, on theoretical grounds, alveolar surfactant plays an important role in the prevention of pulmonary edema (25), and later experimental studies clearly demonstrate that dysfunction of the surfactant system causes pulmonary edema (26,27).

Findings in the present study suggest that surfactant deficiency is also an important factor in the pathogenesis of respiratory insufficiency due to Sendai virus pneumonia. Thirty-six hours after infection, animals showed respiratory insufficiency that could only be overcome by a combination of high ventilatory peak airway pressure and PEEP. These ventilator settings almost completely restored blood gas tensions to normal. However, the fact that endexpiratory pressure—i.e., PEEP—is necessary to prevent alveolar collapse indicates the presence of surfactant deficiency 36 h after infection with Sendai virus.

The decreased thorax-lung compliance 2 days after infection (19) and our present findings that gas exchange can be restored to near normal 48 h after infection by exogenous surfactant are further confirmation of surfactant deficiency in the presence of Sendai virus-induced ARDS.

The surfactant-deficient state observed during Sendai virus pneumonia can be explained in several ways. In viral pneumonia, quantitative surfactant deficiencies are most likely to occur secondary to type

Table 2. Paco2 and pH Values

	Bef	ore	After treatment		After treatment		
	20/0	25/4	5 min	60 min	120 min		
Paco ₂ (mm Hg)							
Surfactant $(n = 9)$	105.8 ± 57.0	95.1 ± 43.6	$61.9 \pm 14.9^{\circ}$	$46.9 \pm 8.2^{\circ}$	$42.6 \pm 8.3^{\circ}$		
Saline $(n = 7)$	74.5 ± 21.0	76.7 ± 17.6	68.1 ± 21.2	$49.2 \pm 12.7^{\circ}$	54.6 ± 15.9		
Untreated $(n = 6)$	122.9 ± 27.1	97.6 ± 23.2	80.≤ ± 11.3	$63.7 \pm 5.3^{\circ}$	55.9 ± 7.3°		
рН							
Surfactant $(n = 9)$	7.13 ± 0.18	7.12 ± 0.16	$7.22 \pm 0.09^{\circ}$	7.33 ± 0.06^{a}	7.33 ± 0.11^{4}		
Saline $(n = 7)$	7.22 ± 0.11	7.19 ± 0.11	7.22 ± 0.14	7.32 ± 0.08^{a}	7.31 ± 0.09		
Untreated $(n = 6)$	7.03 ± 0.05	7.09 ± 0.07	7.13 ± 0.04	7.23 ± 0.03	$7.29 \pm 0.03^{\circ}$		

Values are expressed as mean \pm so and were taken 48 h after infection with a lethal dose of Sendai virus, during artificial ventilation, and after treatment with surfactant, saline, or respiratory support only. Animals were mechanically ventilated with a Siemens 900C ventilator, in a pressure-controlled mode, at a rate of 35/min, I/E ratio of 1:2, and Fro₂ = 1. Different ventilator pressures were applied: $P_{peak} = 20$ cm H_2O (20/0) or $P_{peak} = 25$ cm H_2O with PEEP = 4 cm H_2O (25/4).

Treatment with surfactant or saline was done at 25/4 ventilatory pressures and ventilator settings were kept unchanged during the entire observation period.

*P < 0.05 compared with pretreatment values at the same ventilator settings (25/4).

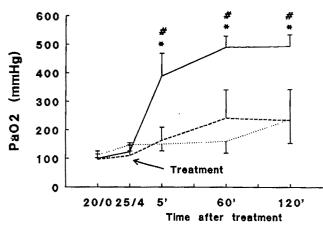


Figure 1. Pao₂ values (mean \pm sD) 48 h after infection with a lethal cose of Sendai virus, during artificial ventilation, and after treatment with surfactant (solid line, n=9), saline (broken line, n=7), respiratory support only (dotted line, n=6). Animals were paralyzed (pancuronium bromide, 0.1 mg/kg IM) and mechanically ventilated with a Siemens 900C ventilator, in a pressure-controlled mode, at a rate of 35/min, I/E ratio of 1:2, and Fro₂ = 1. Different ventilator pressures were applied: $P_{peak} = 20$ cm H_2O (20/0) or $P_{peak} = 25$ cm H_2O with PEEP = 4 cm H_2O (25/4). Treatment with surfactant or saline was done at 25/4 ventilatory pressures and ventilator settings were kept unchanged during the entire observation period. *P < 0.05, surfactant-treated animals versus saline-treated and untreated controls, Mann—Whitney U test. *P < 0.05, versus pretreatment values at the same ventilator settings (25/4).

II cell destruction (16). Destruction of type II cells by the inflammatory reaction to Sendai virus or by virus replication itself may result in depletion of surfactant stores in type II cells and decreased surfactant production by type II cells. Qualitative surfactant deficiency may result from biophysical inhibition of the surfactant material in the alveolar space. Protein-rich edema fluid accumulated in the alveoli of infected animals contains potent inhibitors of the surfactant system, including plasma proteins and red blood cell components. Studies on biophysical inhibition of surfactant activity have demonstrated that whole serum, hemoglobin, and serum proteins such as albumin and fibrinogen can inhibit the function of lung surfactant (28–33). From these studies, it is clear that protein-induced inhibition of surfactant activity is enhanced by low surfactant concentrations. This indicates that the surfactant system in an already surfactant-deficient lung—i.e., a surfactant deficiency as a result of destruction of type II cells by Sendai virus—is especially at risk for biophysical inhibition of surfactant function by the constituents of the alveolar exudate.

Loss of surface active material from the alveolar space via lymphatics or directly into the bloodstream may occur when the integrity of the alveolar-capillary membrane is lost during viral pneumonia. Normally, little surface active material is lost from the lung in this manner, but this situation might change when the alveolar epithelium is disrupted in the presence of lung injury (11,34,35). Furthermore, loss of surfactant-associated proteins by leakage from the alveoli or breakdown of surfactant-associated proteins during the inflammatory reaction to Sendai virus will seriously disturb surfactant function as these proteins are indispensable for proper functioning of the surfactant system (36–40).

Adequate arterial and tissue oxygenation, one of the main goals in treatment of patients with ARDS, can often be achieved by artificial ventilation with PEEP and increased inspiratory oxygen concentrations. In this study, increased ventilatory airway pressures plus PEEP could maintain arterial oxygenation for at least 36 h after infection with the applied

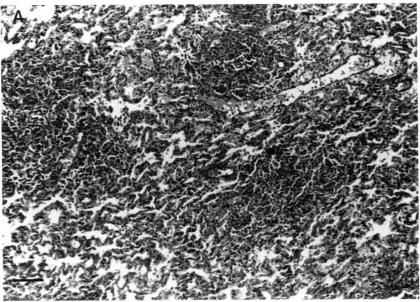
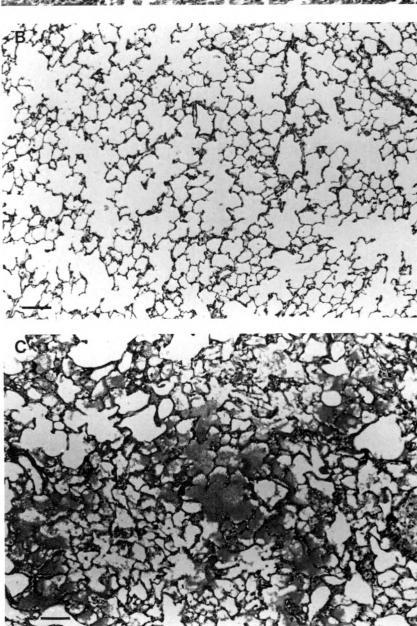


Figure 2. A. Rat lung 48 h after infection with Sendai virus shows pneumonitis, interstitial swelling, alveolar exudate, and atelectasis. Before fixation, lungs were inflated at a pressure of 20 cm $\rm H_2O$. Original magnification = \times 120, hematoxylin/eosin stain. The scale line equals 100 μm. B. Rat lung 48 h after infection with Sendai virus and 2 h after treatment with surfactant and artificial ventilation at 25/4. Before fixation, lungs were inflated at a pressure of 20 cm $\rm H_2O$. Original magnification = \times 120, hematoxylin/eosin stain. The scale line equals 100 μm. C. Rat lung 48 h after infection with Sendai virus and 2 h after treatment with saline and artificial ventilation at 25/4. Before fixation, lungs were inflated at a pressure of 20 cm $\rm H_2O$. Original magnification = \times 120, hematoxylin/eosin stain. The scale line equals 100 μm.



ventilator settings. After 48 h, however, high inspiratory peak pressures together with PEEP (25/4) resulted in only minor (20%) increases in Pao_2 (n=22), compared with low inspiratory peak pressure without PEEP (15/0). This can be explained by alveolar collapse resulting from increased intrapulmonary surface tensions. Higher peak airway pressures are needed to open up the lungs and a PEEP of 4 cm H_2O is not high enough to prevent end-expiratory collapse, demonstrating the small benefits of the applied ventilatory strategy.

Instillation of surfactant almost instantaneously increased Pao₂ significantly (320% increase within 5 min), and during subsequent observation for 2 h Pao₂ increased even further. In the saline-treated and in the nontreated control groups, Pao₂ gradually increased whereas Paco₂ gradually decreased during the observation period, probably due to the application of PEEP.

Our findings indicate that, initially, a surfactant-deficient state and resulting hypoxemia in the acute phase of viral pneumonia can be overcome by application of PEEP. In a later stage of the disease, however, a higher peak airway pressure with PEEP has no significant effect because the opening pressure of the lungs is increased. Intratracheal instillation of exogenous surfactant, however, reduces the opening pressure, prevents alveolar collapse, and, combined with ventilatory support, restores gas exchange to almost normal.

We conclude that lethal infection with Sendai virus in rats results in a surfactant deficiency of the lungs, which, initially, can be treated with respiratory support with high peak airway pressures and PEEP. When respiratory insufficiency is fully developed, artificial ventilation at high airway pressures with PEEP is not sufficient to restore gas exchange. At this stage of the disease, however, intratracheal instillation of exogenous surfactant can almost completely restore gas exchange to normal.

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Effect of Halothane on Arrhythmogenic Responses Induced by Sympathomimetic Agents in Single Rat Heart Cells

Rhonda L. Zuckerman, MD, and David M. Wheeler, MD, PhD

ZUCKERMAN RL, WHEELER DM. Effect of halothane on arrhythmogenic responses induced by sympathomimetic agents in single rat heart cells. Anesth Analg 1991;72: 596–603.

The combination of catecholamines and halothane has long been recognized as arrhythmogenic. The purpose of this study was to evaluate whether the mechanism of this interaction originates at the single cell level. The incidence of spontaneous contractile waves occurring between stimulated beats (interbeat waves), early aftercontractions, and late aftercontractions was measured in rat myocytes exposed to sympathomimetics with and without halothane. Each of these endpoints in single cells has the potential to produce arrhythmias in multicellular preparations. Interbeat waves and late aftercontractions were observed with isoproterenol $(1 \times 10^{-7} \text{ M})$ and norepinephrine $(1-3 \times 10^{-7} \text{ M})$. The

incidence of these phenomena was significantly reduced in the presence of 0.30 mM halothane. Early aftercontractions occurred in the presence of isoproterenol (1 \times 10 $^{-7}$ M), norepinephrine (1–3 \times 10 $^{-7}$ M), and phenylephrine (5–10 \times 10 $^{-6}$ M). There was a statistically significant decrease in the incidence of early aftercontractions in the presence of 0.30 mM halothane. These results indicate that the mechanism behind the clinically observed increased arrhythmogenicity of catecholamines with halothane does not arise at the level of single ventricular cells because halothane inhibited sympathomimetic-induced arrhythmogenic activity in this model. The probable mechanisms rather include altered impulse propagation, which might lead to phenomena such as reentry.

Key Words: ANESTHETICS, VOLATILE—halothane. HEART, ARRHYTHMIAS—halothane.

The arrhythmogenic effect of catecholamines is intensified in the presence of halothane (1). The purpose of this study was to determine if the origin of this interaction lies at the single cell level. Several mechanisms of arrhythmia production have their origins in certain phenomena that occur in individual cardiac cells. Such phenomena occur independently of cellto-cell conduction (impulse propagation) even though they may contribute to altered cardiac conduction. One example is spontaneous contractile waves. These waves are distinct from normal synchronous contractile activity and are caused by localized Ca²⁺ release from the sarcoplasmic reticulum (SR) (2). Such waves are observed in resting rat cardiac myocytes at physiologic extracellular Ca²⁺ concentrations. Stimulation of the myocytes at 60 beats/min typically suppressed these contractile waves. Environmental changes that lead to the appearance of waves between stimulated beats indicate an increase in spontaneous Ca²⁺ release from the SR and are usually associated with an increase in total intracellular Ca²⁺. These interbeat waves (IBWs) can attenuate the subsequent beat and in some circumstances lead to the generation of spontaneous action potential and thus have arrhythmogenic potential (3) (Figure 1). Triggered activity is another arrhythmogenic mechanism that can be observed in single cardiac cells. Triggered activity includes early aftercontractions (EACs) and late aftercontractions (LACs), the mechanical correlates of the similarly named depolarizations (4). Late aftercontractions are contractions, usually smaller than normal, that occur when a sequence of stimulated beats ceases (Figure 2). Early aftercontractions occur during the relaxation phase of a normal contraction and may appear as an ectopic contraction, or as a failure of the initial beat to completely relax, or both. The following stimulated beat may be attenuated or dropped completely (Figure 3). To determine whether halothane-catecholamine arrhythmias might be initiated by such cellular

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INTER-BEAT WAVES

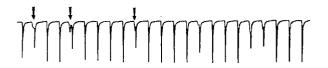


Figure 1. Continuous recording of cell length in a single rat heart cell paced at 60 beats/min and exposed to 0.30 mM halothane and 3×10^{-7} M norepinephrine. Interbeat waves are evident in this tracing. Examples are marked by *arrows*. Note that the beat after each IBW is attenuated.

LATE AFTERCONTRACTIONS



<u>Figure 2</u>. Cell length tracing of the end of a 60-beat train of stimuli with three LACs (marked by *arrows*) that occur after the last paced beat (*). Isoproterenol (1 \times 10⁻⁷ M) present in superfusate.

EARLY AFTERCONTRACTIONS



<u>Figure 3</u>. A train of beats in the presence of 0.30 mM halothane and 5×10^{-8} M isoproterenol demonstrating EACs associated with many of the paced beats.

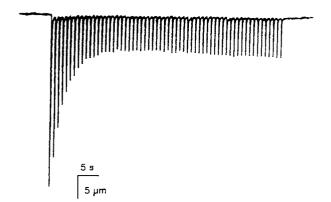
events, we investigated the effect of combinations of halothane and sympathomimetic agents on single rat heart cells.

Methods

The protocol was approved by the institutional animal care and use committee. Male 2–4-mo-old Wistar or Sprague–Dawley rats were used. In some experiments, rats were decapitated by guillotine and the hearts rapidly excised. In others, rats were anesthetized with pentobarbital (0.5 mL of a 65-mg/mL solution intraperitoneally) and the hearts were excised as soon as the response to tail clamp was lost. There was no difference in yield of viable ventricular myocytes associated with the different techniques of killing the animals. Cells were isolated using the collagenase perfusion technique previously described (5).

Briefly, after excision the heart was placed in a Petri dish and the aortic root was cannulated. The coronary arteries were then perfused by gravity with a nominally Ca²⁺-free Earle's salt solution until the blood was cleared and then with a collagenase/ protease solution (1 g/L collagenase, type B, Boringer/ Mannheim; 0.04 g/L protease, Sigma Chemical Co., St. Louis, Mo.; 50 µM CaCl₂ added) for approximately 15 min. The perfusate was kept at 37°C and was gassed with 95% O₂/5% CO₂ to maintain pH at 7.35 ± 0.05 . The enzymes were washed out using a 5-min perfusion with an Earle's salt solution containing $100 \mu M \text{ Ca}^{2+}$. Perfusion was then discontinued, the ventricles were finely minced with scissors, and the tissues were agitated with a pipet and then strained through a 200- μ m mesh. Resuspension was done initially in a solution containing $250 \mu M \text{ Ca}^{2+}$, 137 mM Na⁺, 144 mM Cl⁻, 5.6 mM dextrose, 5.4 mM K⁺, 1.2 mM MgSO₄, 1 mM NaH₂PO₄, and 20 mM HEPES, adjusted to pH 7.4 at room temperature. The cells were then transferred to another vial containing the same solution but with 500 μ M CaCl₂, and then to one containing 1 mM CaCl₂. The cell suspension was divided into 2-mL aliquots, stored in loosely covered polyethylene vials, and kept in an incubator at 37°C. For each experiment, 20 μ L of cell-containing solution was placed in a chamber and the cells were allowed to stick to the glass bottom. The chamber was then perfused with the HEPES-buffered salt solution having a Ca²⁺ concentration of 1 mM. The solution was warmed before entering the cell chamber so that the temperature within the chamber remained at 36.5 \pm 0.5° C. For each experiment, one cell from the $20-\mu$ L sample was observed and its length was measured using methods previously reported (6) and briefly described below.

The chamber was mounted on an inverted Diavert microscope (E. Leitz, Rockleigh, N.J.), and cell length was continuously measured by projecting the cell



<u>Figure 4</u>. Typical negative staircase obtained when 60 beats of field stimulation are given to a rat ventricular myocyte in a balanced salt solution with 1 mM Ca²⁺ buffered with 20 mM HEPES.

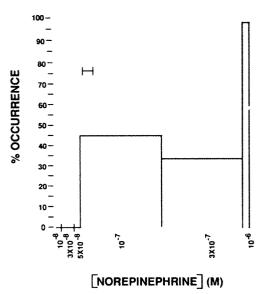
image on a photo diode array aligned with the long axis of the cell. Electrical field stimulation was applied via platinum wire electrodes at the two ends of the chamber, and cell length was continuously recorded during contractions. The cell being studied was viewed on a video monitor, and only cells having the following qualities were used (5): rodlike in shape, sharp edges, and no intracellular blebs. In addition, each cell studied was first given a train of 60 beats to ensure that its contraction pattern was that of a normal rat ventricular myocyte (Figure 4).

Once a cell was judged appropriate for study, its environment was changed by switching solutions and in some cases the overlying gas as well. Solutions either contained halothane, a sympathomimetic agent plus halothane, or a sympathomimetic agent without halothane. For halothane-containing solutions, 2.5% halothane in air was bubbled at room temperature through a flask containing the above salt solution plus or minus a sympathomimetic agent, and both the solution and the overlying gas from this flask were directed to the chamber. The concentration of halothane in the cell chamber achieved by this method was approximately 0.30 mM as measured by gas chromatography. This concentration converts to 0.9 vol% using a partition coefficient of 0.83 (7). A loss of halothane between solution reservoir and cell chamber clearly occurred. The concentration of halothane in the chamber was essentially independent of time after change of solution because the halothane-containing solution continuously flowed through all perfusion components whether it was directed to the cell chamber or not. The switching valve was located just before the chamber inlet.

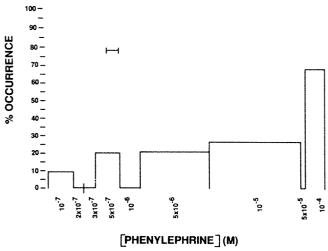
For plain sympathomimetic-containing solutions, the drug was added to a flask containing the above salt solution, and this was directed to the chamber along with overlying room air. One of the two following protocols was followed for exposing the cell to different solutions: (a) the cell was exposed to a sympathomimetic agent, then the sympathomimetic agent plus halothane, then the sympathomimetic agent alone again; or (b) the cell was exposed to halothane alone first, then halothane plus a sympathomimetic agent, then the sympathomimetic agent, then halothane plus the sympathomimetic agent again. Once either protocol was started, the transitions between solutions were repeated several times. During these transitions, electrical field stimulation was applied as follows. In some experiments, in each solution the cells were stimulated with trains of 60 beats at 1 beat/s, with the trains separated by several minutes of rest. In other experiments, stimulation at 1 beat/s was continued during transitions between the solutions, transitions only being made after a steady state was achieved in each solution. A steadystate interval was defined as a ≥20 s period occurring at least 2 min after a transition and during which time the amplitude of contractions was constant. Measurements of the number of IBWs, the duration of EACs (if present), and the presence or absence of LACs were made in each solution (LACs could only be present at the end of a train, when stimuli were interrupted). In the case of measurements during continuous beating, 20-s intervals (20 beats) at steady state as defined above were sampled for IBWs and EACs.

The sympathomimetic agents used included phenylephrine, isoproterenol, and norepinephrine because they possess α -, β -, and mixed-adrenergic properties, respectively. Initially, crude doseresponse curves were generated for each sympathomimetic alone to determine what concentration to use for further study (Figures 5–7). At concentrations lower than those used, few arrhythmogenic phenomena were observed; at concentrations higher than those used, the cells became unstable, exhibiting irreversible contractile activity. In addition to those using the above agents, experiments were done in which cells were exposed to norepinephrine plus specific blockers to rule out any nonspecific effects of isoproterenol or phenylephrine. Propranolol was used for β -blockade and prazosin plus yohimbine for α -blockade.

The data were analyzed as follows. Each of the endpoints (IBWs, EACs, LACs) was considered independently. Because the effect of halothane was of primary interest, pairs of observations were formed by grouping a result from a cell in sympathomimetic agent alone to the first comparable result in sympathomimetic agent plus halothane after transition of

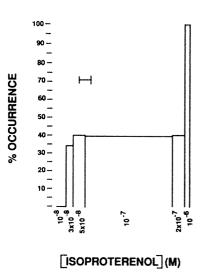


<u>Figure 5</u>. Dose-response curves for sympathomimetic solutions. Percent occurrence of IBWs with norepinephrine. Width of bar is proportional to number of cells studied at that concentration. Calibration bar equals five cells. These data were generated from studies on 29 cells from 11 rats.



<u>Figure 6</u>. Dose-response curves for sympathomimetic solutions. Percent occurrence of EACs with phenylephrine. Width of bar is proportional to number of cells studied at that concentration. *Calibration bar* equals five cells. These data were generated from studies on 29 cells from 13 rats.

solutions. Pairs of results were also formed from data on opposite sides of a transition from sympathomimetic agent plus halothane to sympathomimetic agent alone. Pairs were formed only from observation of the same cells, and those observations were taken from times as near as possible to the solution transition, given the minimum 2-min allowance for equilibration in a new solution. In the case of IBWs, the difference in number of waves between the paired test intervals was calculated. Pairs in which no waves



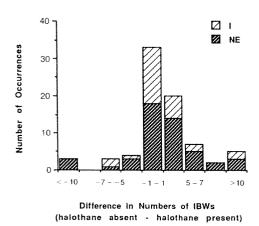
<u>Figure 7</u>. Dose-response curves for sympathomimetic solutions. Percent occurrence of LACs with isoproterenol. Width of bar is proportional to number of cells studied at that concentration. *Calibration bar* equals five cells. These data were generated from studies on 24 cells from 10 rats.

occurred in either condition were dropped from the analysis. Because the data were not normally distributed, all analyses were nonparametric. A Mann-Whitney U-test was used to determine whether there was a significant difference based on the order in which the solutions were applied. The significance of the effect of halothane was determined using the Wilcoxon rank sum test. To consider whether the effect of halothane could be attributed to specific subgroups of observation the Kruskal-Wallis test was used. The effect of halothane on the duration of EACs was determined using the same steps as for IBWs. The presence or absence of LACs after a train of beats was analyzed in pairs originating from the same cell on opposite sides (temporally) of a transition into or out of halothane in the presence of sympathomimetic agent. The number of pairs in which LACs occurred in sympathomimetic agent alone but not in sympathomimetic agent plus halothane were then compared with the number of pairs exhibiting the opposite result.

Results

In the case of IBWs and EACS, initial analysis revealed that there were no significant differences in results between experiments in which transitions were made from halothane-containing solutions to halothane-free solutions and experiments in which solutions were applied in the opposite order. The observations were therefore pooled. Figure 8 illus-

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<u>Figure 8</u>. Frequency histogram characterizing the incidence of differences in number of IBWs occurring in the presence of sympathomimetic solutions with and without 0.30 mM halothane. Each difference was derived from a single cell by comparing IBWs during 20-s steady-state intervals or during 60-beat trains. 1, isoproterenol; NE, norepinephrine. These data were generated from studies on 37 cells from 16 rats.

trates the difference in number of IBWs between each paired observation; that is, between either two trains or two steady-state intervals temporally separated by a solution transition during which halothane was either added or subtracted. The amount of each of these differences fell into one of the intervals marked on the abscissa. Positive values correspond to pairs in which more IBWs were present in halothane-free solutions than in halothane-containing solutions. The number of differences falling into each interval, or number of occurrences, constitutes the ordinate. The resulting frequency histogram reveals that although most of the differences were close to zero, positive values were more commonly obtained than negative, and the Wilcoxon rank sum test indicates that there is a significant decrease in the number of IBWs in halothane-containing sympathomimetic solutions compared to sympathomimetic solutions alone. No differences between subgroups could be detected. That is, the overall difference related to halothane did not appear to originate from results with a specific sympathomimetic or from trains as opposed to steady-state intervals. Results are shown for isoproterenol and norepinephrine but not for phenylephrine because IBWs did not occur in cells exposed to phenylephrine with or without halothane.

Figure 9 illustrates the results of the same paired analyses for EACs. The differences in amount of time of EACs for each paired observation are grouped into intervals, and the number of these differences in each interval is shown. Again, the majority of differences are small, falling into the center bar. However, as with IBWs, the preponderance of positive rather than negative values when a difference is seen indicates

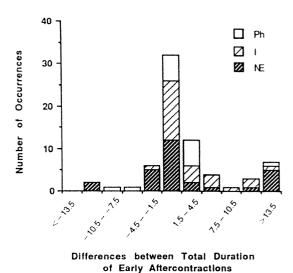


Figure 9. Frequency histogram characterizing the incidence of differences in the duration (in seconds) of EACs occurring in the presence of sympathomimetic solutions with and without 0.30 mM halothane. Each difference was generated from a single cell by subtracting the total duration of EACs during a 20-s steady-state interval or 60-beat train in the presence of halothane plus sympathomimetic solution from the total duration during a comparable interval in sympathomimetic solution alone. Ph, phenylephrine; I,

isoproterenol; NE, norepinephrine. These data were generated

from studies on 52 cells from 25 rats.

(halothane absent - halothane present)

that EACs occur more frequently in non-halothanecontaining sympathomimetic solutions than in those containing halothane. This result was found to be statistically significant. No differences between the results for different sympathomimetic solutions (subgroups) were detected.

Table 1 shows the results used for the sign test analysis of the presence or absence of LACs after trains of stimuli were given to cells exposed to sympathomimetic solutions with or without halothane. Paired observations from single cells undergoing solution transitions were used (as was done for the IBW and EAC analyses). The number of paired observations in which LACs occurred in sympathomimetic solution alone but not in sympathomimetic solution plus halothane was significantly greater than the number of pairs in which LACs occurred only in the halothane-containing solution. As was seen with IBWs and EACs, the incidence of LACs was lower in the presence of halothane.

The results of experiments done using norepinephrine plus specific α -blockers are shown in Table 2. The data are grouped and unpaired, and although the trend is toward a decrease in incidence of IBWs, EACs, and LACs in the presence of halothane, there was no statistically significant difference in incidence of these phenomena in halothane-containing and

<u>Table 1</u>. Numbers of Paired Observations^a for Late Aftercontractions in the Presence and Absence of 0.30 mM Halothane

	I	NE	Ph
Present with and without halothane	4	9	0
Not present with and without halothane	10	8	14
Present without halothane/not present with halothane ^b	3	5	1
Not present without halothane/present with halothane	a	0	0

I, isoproterenol; NE, norepinephrine; Ph, phenylephrine.

These data were generated from studies on 35 cells from 20 rats.

Each pair originates from two trains of beats in a single cell—one train in the presence of sympathomimetic solution alone, the other in the presence of sympathomimetic solution plus halothane.

When results from the three sympathomimetic solutions are combined, the two groups of discordant pairs are significantly different (P < 0.05) by the sign test. That is, the incidence of late aftercontractions without halothane is greater than that with halothane.

<u>Table 2</u>. Incidence of Arrhythmogenic Phenomena in the Presence of 1×10^{-6} M Norepinephrine plus 1×10^{-6} M Prazosin and 1×10^{-6} M Yohimbine

IBWs	No H	7/14
	Н	6/14
EACs	No H H	3/14 1/14
LACs	No H H	4/6 2/5

EAC, early aftercontractions; IBWs, interbeat waves; LACs, late after-contractions.

Data for each condition are shown as (number of trains or steady-state intervals with events)/(total number of trains or steady-state intervals).

These data were generated from studies on four cells from two rats.

non-halothane-containing solutions. In no case were more arrhythmogenic events seen in cells exposed to halothane plus 10^{-6} M norepinephrine combined with 10^{-6} M prazosin and 10^{-6} M yohimbine than in those exposed to norepinephrine plus the α -blockers alone. Cells exposed to 10^{-6} M norepinephrine plus 10^{-6} M propranolol with or without halothane did not exhibit any arrhythmogenic phenomena. This lack of arrhythmogenic activity during this α -stimulation was expected because phenylephrine induced arrhythmogenic phenomena only when used in high concentrations.

Discussion

The clinical observation that halothane can potentiate catecholamine-induced ventricular arrhythmias has been well documented (1). However, the physiologic level at which this phenomenon occurs remains obscure (8). Mechanisms of cardiac arrhythmias have

been generally categorized as those affecting impulse generation such as altered automaticity or triggered activity, or those that affect impulse propagation (4). Although impulse propagation cannot be studied at the single cell level, events that are potentially arrhythmogenic can be observed in single cells. These events—IBWs, EACs, and LACs—are believed to be related to arrhythmias observed in intact tissue (3,4). These phenomena have been observed in single cells exposed to sympathomimetics alone (9). In our study, 0.9 vol% halothane inhibited the development of these phenomena. This was seen with α -, β -, and mixed-adrenergic stimulation directly or by selective blockade of a mixed agent. In addition, this outcome was consistently found over a range of sympathomimetic concentrations designed to give meaningful and reproducible responses—with lower concentrations producing little to no arrhythmogenic activity and higher concentrations producing unpredictable cell shortening and contracture. The range of concentrations used in our experiments corresponds to the in vivo concentrations measured in animals receiving arrhythmogenic doses of these agents. Metz and Maze noted that the threshold concentration of epinephrine needed to induce arrhythmias in halothaneanesthetized dogs was approximately 70 ng/mL or 3.8×10^{-7} M (10). In our model, the concentration of norepinephrine used was comparable at 1-3 \times $10^{-7} M.$

Using multiple preparations, other investigators have demonstrated both decreased automaticity and decreased triggered activity in the presence of halothane. In a study of canine Purkinje fibers, halothane reduced the slope and antagonized the enhancement of phase 4 depolarization by epinephrine (11). In ischemic canine Purkinje fibers, exposure to halothane resulted in decreased automaticity (12). Decreased automaticity has also been observed in the SA node in the presence of halothane, manifested by a decrease in the slope of phase 4 of the action potential (13). Similarly, examination of rabbit SA node strips revealed that halothane decreased the velocity of diastolic depolarization (14). There is also evidence that halothane suppresses triggered activity. Halothane has been shown to inhibit the generation of aftercontractions in depolarized ventricular fibers exhibiting slow action potentials (15). Exposure to halothane decreased the amplitude of late afterdepolarizations that occurred in the setting of ischemia (12). It has been noted that the amplitude of ouabaininduced delayed afterdepolarizations was decreased in the presence of halothane (16). Our study indicates that sympathomimetic-induced triggered activity is also inhibited by halothane.

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In contrast to these observed effects of halothane on automaticity and triggered activity, where it has properties more like that of an antiarrhythmic agent, studies of its effects on impulse propagation reveal characteristics that might explain its arrhythmogenic potential. Slowed conduction from the atrium to the His bundle (P-H interval), as well as a lesser slowing of conduction in the ventricle (H-V interval), has been observed in the presence of halothane (17). Slowed conduction and abbreviated refractoriness was also demonstrated in other studies (18,19). The potential for reentry phenomenon was further explored in ischemic tissue, where halothane was shown to accentuate repolarization differences between proximal nonischemic and distal ischemic Purkinje fibers in a canine model (12). In isolated guinea pig ventricular cell pairs, halothane exposure induced decreased electrical coupling. This decreased conduction across gap junctions in the presence of halothane might predispose to reentry arrhythmias in vivo (20).

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It has been proposed that the decreased automaticity/triggered activity seen with halothane may be secondary to the same mechanism of action that leads to decreased myocardial contractility (21). Halothaneinduced changes in K⁺, Na⁺, and/or Ca²⁺ flux across cell membranes have been suggested as possible significant effects (12,19). Depression of slow channel Ca^{2+} entry (22–25), altered function of the Na⁺/Ca²⁺ exchange pump, and reduction of the Ca2+ content of the SR (6,26), factors considered significant in the negative inotropic effect of halothane, may also contribute to decreased automaticity/triggered activity. In a study on human atrial fibers, both force of contraction and extent of epinephrine-induced triggered activity were inhibited by halothane. In this study these effects of halothane were partially mimicked by Ca2+ and Na+ channel blockers, suggesting that halothane's antiarrhythmic as well as antiinotropic effect might be due to reduction of ion fluxes across the cell membrane (21). The mechanisms of induction of aftercontractions and IBWs have been studied in intact tissue and individual cells and have been linked to intracellular Ca2+ concentration changes, either secondary to increases in L-type Ca²⁺ transmembrane current (27) or in Ca2+ released from the SR (6,26). Because continued exposure to halothane reduces both slow inward Ca2+ current and SR Ca2+ release (presumably secondary to the decreased SR Ca2+ load), it would oppose these mechanisms. Therefore, the apparent inhibitory action of halothane on triggered activity and IBWs probably has its basis in Ca²⁺ metabolism.

The role of specific adrenergic receptors in halothane/sympathomimetic arrhythmogenesis has

been previously studied in several intact animal models. Maze et al. used selective adrenergic receptor blockade in dogs anesthetized with halothane and exposed to epinephrine to determine if α - or β -receptor activity was more associated with ventricular arrhythmias. Their results supported the predominant role of α_1 -adrenergic agonists in halothane/ sympathomimetic-induced arrhythmias (28,29). This was in contrast to earlier observations implicating β -adrenergic stimulation (1) and the clinical observation of more frequent arrhythmias after administration of β -agonists (both of which partially may be due to non-receptor-specific effects). In our study, little arrhythmogenic activity was seen in cells exposed to α -adrenergic agents with or without halothane. Early aftercontractions during trains of stimulation were the predominant event noted during phenylephrine exposure. β -Adrenergic or mixed-adrenergic agent exposure resulted in more arrhythmogenic events overall. Again, whether α -, β -, or mixed-adrenergic agents were used, the addition of halothane suppressed IBWs, EACs, or LACs. Therefore, the aspect of α -stimulation that promotes halothane-associated arrhythmias does not involve these mechanisms.

In conclusion, the widely noted in vivo synergistic arrhythmogenicity of the halothane/catecholamine combination was not observed in our isolated ventricular myocyte model. Neither automaticity nor triggered activity was increased by this combination in single ventricular cells. Therefore, the mechanism for this synergy probably arises from abnormal impulse propagation.

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Effects of Nitrous Oxide on Coronary Pressure and Regional Contractile Function in Experimental Myocardial Ischemia

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CASON BA, DEMAS KA, MAZER CD, GORDON HJ, HICKEY RF. Effects of nitrous oxide on coronary pressure and regional contractile function in experimental myocardial ischemia. Anesth Analg 1991;72:604–11.

To determine whether nitrous oxide (N_2O) worsens myocardial ischemia by diminishing coronary pressure, we performed two sets of experiments using an acutely instrumented swine model of regional coronary ischemia. In constant pressure experiments (n=11), coronary pressure and heart rate were kept constant as N_2O (77%–79%) was substituted for N_2 in the inspired gas. Nitrous oxide decreased systolic shortening, measured by sonomicrometry, from 68.0% to 63.6% (P<0.05) of preischemic control values in the ischemic zone and from 116.2% to 103.2% (P<0.05) of control values in the adjacent normal myocardium. There was no disproportionate effect of N_2O on ischemic myocardium, and the N_2O -induced depression of contractile function was fully reversible.

In a series of constant external stenosis experiments (n = 13), the effects of N₂O on heart rate, mean arterial pressure,

and the coronary stenosis itself were not controlled. In these experiments, substitution of N2O for N2 induced deterioration in both the ischemic zone (systolic shortening decreased from 68.7% to 58.4% of preischemic control values, P < 0.05) and in the adjacent normal myocardium (systolic shortening decreased from 113% to 102.9% of preischemic control, P < 0.05). Nitrous-oxide-induced ischemic zone contractile dysfunction was often not reversible. The pressure gradient across the coronary stenosis did not increase and peripheral coronary pressure did not decrease because of N₂O. Diffusion hypoxia was also excluded. This study confirms that N2O has a significant but mild depressant effect on the performance of both normal and ischemic myocardium. Additionally, N₂O administration can initiate progressive deterioration of contractile function, probably ischemic, which is mediated by small changes in hemodynamic parameters, rather than by direct coronary effects.

Key Words: ANESTHETIC, GASES—nitrous oxide. HEART, BLOOD FLOW—ischemia, ventricular function.

The use of nitrous oxide (N_2O) in the anesthetic management of patients with ischemic heart disease is debated. Because of its reputation for having minimal cardiovascular depressant effects, N_2O has long enjoyed favored status as a component of general anesthesia. As the most commonly used inhaled anesthetic in the United States (1), N_2O is frequently and safely used even in the setting of coronary artery disease (2,3). Because of its sedative and analgesic

cular depression, nitrous oxide has even been used for treatment of acute myocardial ischemia and infarction (4,5). On the other hand, anesthesia with N_2O has been reported to cause substantial myocardial depression (6-11) and even cardiovascular collapse (12). In patients with limited cardiac reserve and in those with blunted or already maximal sympathetic nervous system activity, N_2O can diminish myocardial contractile performance, decrease cardiac output, blood pressure, and myocardial oxygen delivery, and can, because of these hemodynamic effects, cause coronary hypoperfusion, regional or global myocardial ischemia (8,9), and cardiovascular collapse (12).

effects and because of its alleged minimal cardiovas-

Additionally, Philbin et al. have reported that N₂O induces ischemic myocardial wall motion abnormalities in dogs with critical coronary stenoses, and that this ischemia is not caused by N₂O-induced hypoxemia or hemodynamic changes (13). Subsequent in-

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vestigation of this finding by Nathan has shown that, in dogs, although N₂O does not worsen ischemia when hemodynamics are controlled and hypoxia is avoided (14), very small N₂O-induced changes in systemic hemodynamics aggravate preexisting ischemia (15). The studies of Nathan, however, utilized isolated coronary perfusion and a stenosis of the extracorporeal silastic perfusion circuit, which would not be subject to N₂O-induced changes at the stenotic site as would in situ coronary artery stenoses. Several questions regarding the effects of N₂O on in vivo coronary stenoses, owing to possible effects of N₂O on coronary pressure and dynamic effects at the in vivo stenosis site, are therefore unanswered.

To determine whether N₂O worsens myocardial ischemia by diminishing coronary pressure, we performed two sets of experiments in acutely instrumented swine. First, to determine whether N₂O worsens myocardial ischemia when coronary pressure is held constant, we used a swine model of regional coronary ischemia. In these constant coronary pressure experiments, the coronary pressure was kept constant throughout the experiment by means of a variable coronary occluder. We measured the effects of the substitution of 75%–78% N₂O for an equivalent inspired concentration of N₂O on regional wall motion using sonomicrometry. In a second series of experiments, we sought to determine whether N₂O causes harmful decrements in coronary pressure. We used a similar model of regional ischemia, but with the modification that a constant external stenosis was applied directly to the coronary artery. Dynamic coronary effects of N₂O, such as direct humorally mediated constriction at the stenotic site or pressureinduced passive collapse of the stenotic site, would therefore still be possible. In these constant external stenosis experiments, we measured the effects of N₂O on regional wall motion and on the gradient between mean aortic and coronary pressure, a measure of the hemodynamic significance of the stenosis.

Methods

Anesthesia and Surgery

After approval by our committee on animal welfare, two sets of experiments were performed, each utilizing slightly different anesthetic procedures. In all experiments, pigs were initially anesthetized with isoflurane for the surgical preparation, then were converted to a barbiturate/narcotic anesthetic for the experimental study. Isoflurane was discontinued at least 1 h before each experimental study.

In the first set of experiments (constant coronary

pressure), 11 pigs were anesthetized with isoflurane (1%-2.5%) by inhalation. After orotracheal intubation and mechanical ventilation, a 75%-78% nitrogen/ oxygen mixture was initiated. F102 was measured by mass spectrometry (Perkins-Elmer) and was adjusted to provide an arterial Po₂ of 90–110 mm Hg. Minute ventilation was adjusted to maintain normal arterial Pco₂. Arterial blood gas tensions were measured using a Radiometer ABL-II system (Radiometer, Copenhagen, Denmark). After the surgical preparation and instrumentation were complete, isoflurane was discontinued and an intravenous barbiturate/ narcotic anesthetic regimen was substituted. Each pig was given a loading dose of pentobarbital (25 mg/kg) and of fentanyl (50 μ g/kg), followed by a maintenance fentanyl infusion of 0.5 μ g·kg⁻¹·min⁻¹.

In the second set of experiments (constant stenosis), 13 pigs were anesthetized with isoflurane, as in the first group. Pigs in the constant stenosis group were given a larger loading dose of fentanyl (100 μ g/kg), and a higher constant infusion rate (0.75 μ g·kg⁻¹·min⁻¹), but received the same loading dose of pentobarbital (25 mg/kg) as those in the constant pressure group.

Instrumentation

In each pig, a median sternotomy was performed. Then, as prescribed by the particular experimental protocol, one of two types of coronary stenosis was produced in the left anterior descending coronary artery (LAD) near its origin. In the constant pressure experiments, an adjustable pneumatic occluder (manufactured in our laboratory) was used. In the constant external stenosis experiments, a precisely adjustable screw-driven clamp made of stainless steel was used (Selverstone clamp, Codman Instruments). To measure regional systolic shortening (SS), 2-mm piezoelectric crystals (Dimension 3, La Jolla, Calif.) were inserted in the inner third of the myocardium of the LAD and circumflex coronary artery (CX) territories, parallel to the short axis of the heart (16,17). A 16-gauge catheter was inserted through the common carotid artery into the aorta for measurement of blood pressure by strain-gauge pressure transducer (Gould). A 7F micromanometer-tip catheter (Millar Instruments, Houston, Tex.) was inserted through the left atrial appendage into the left ventricle to measure left ventricular pressure and to provide a timing signal for sonomicrometry measurements. A small 25-gauge catheter was inserted retrogradely into the LAD coronary artery (18) to measure mean LAD coronary artery pressure. In the constant pressure experiments only, atrial pacing was instituted at a rate 20% above resting heart rate.

Constant pressure protocol. In these experiments the stenosis was created by means of the screw-driven pneumatic occluder filled with air. To induce mild ischemia in the LAD zone, the screw-driven balloon occluder was gradually inflated until the LAD myocardium showed diminished SS, but neither akinesis nor bulging. The LAD pressure causing this level of dysfunction was recorded, and the occluder was subsequently adjusted as necessary to keep the coronary pressure constant at this level. The degree of ischemic dysfunction was then allowed to stabilize at this constant coronary pressure. Systolic shortening was measured every 5 min during this stabilization period, and ischemic dysfunction was considered to be stable when three consecutive measurements varied by no more than 5%. Then, measurements of hemodynamics and of LAD and CX segmental function were made every 5 min during 15 min of continued nitrogen (N_2) administration, $F_{102} = 0.21$ to 0.23 (sufficient to keep baseline Po_2 85–100). N_2O (77%– 79%) was rapidly substituted for N_2 in the inspired gas, and sequential measurements were again made every 5 min during 15 min of N_2O exposure. Then N_2 (77%–79%) was resumed, and final measurements were made every 5 min for another 15 min. During the first 4 min of N₂O washout, arterial Po₂ was measured every minute to rule out hypoxia caused by the washout of N_2O (19,20).

Constant external stenosis protocol. In these experiments, the coronary stenosis was created by compressing the LAD coronary artery between two flat metal plates in a precisely adjustable screw-driven clamp. The stenosis was tightened until the LADperfused myocardium showed diminished SS but not akinesis or bulging. Measurements of SS were then made every 5 min until three consecutive measurements varied by no more than 5%, which was considered to be stable ischemic dysfunction. The LAD pressure causing this level of dysfunction was recorded, but the occluder was not subsequently adjusted at any time. Measurements of hemodynamics and of LAD and CX segmental function were then made every 5 min during 15 min of continued N₂ administration, $F_{102} = 0.21$ to 0.23. An equivalent concentration of N₂O was rapidly substituted for N₂ in the inspired gas, and sequential measurements were again made every 5 min during 15 min of N₂O exposure. Nitrous oxide was then discontinued, N₂ was resumed at the original concentration, and final measurements were made every 5 min for another 15 min. During the first 4 min of N_2O washout, arterial Po_2 was measured every minute to rule out hypoxia caused by the washout of N_2O (19,20).

Data Analysis

For sonomicrometric measurements, end-diastole was defined as the time of the initial upstroke of the left ventricular systolic pressure trace, and end-systole was defined as the time of peak negative left ventricular dP/dt (21). Regional systolic shortening was then calculated as

SS (%) =
$$\frac{\text{(End-diastolic length)} - \text{(End-systolic length)}}{\text{(End-diastolic length)}} \times 100$$

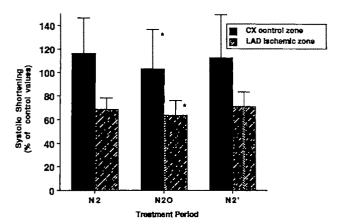
for both myocardial zones and was expressed as a percentage of the prestenosis value in each zone. Results were analyzed by repeated-measures analysis of variance, and the Newman–Keuls test or paired t-tests were used where appropriate. Because analysis of variance revealed no significant differences in hemodynamics or systolic shortening within any of the 15-min periods of N_2 or N_2 O administration, each 15-min set of three observations has been averaged in each individual for clarity of presentation. Thus, each experimental point (hemodynamics and SS) represents the mean of three consecutive and closely spaced measurements. All data are expressed as mean \pm sD, and P values <0.05 were considered to be statistically significant.

Results

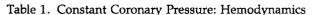
Constant Pressure Experiments

Baseline preischemic SS was $21.5\% \pm 6.2\%$ in the LAD-perfused zone and $14.9\% \pm 4.8\%$ in the control CX zone. After induction of stable LAD ischemia, SS was reduced to 68% of control values in the LAD zone (Figure 1). Systolic shortening in the adjacent normal myocardium became supranormal (116.2% of control CX shortening) (Figure 1). The substitution of 77%-79% N₂O for N₂ in the inspired gas mixture diminished the SS slightly in both normal and ischemic myocardium (to 103.2% and 63.6% of preischemic values, respectively, both significant at P <0.05). There was no disproportionate effect on the ischemic zone. Mean arterial pressure did not change significantly with the substitution of N_2O for N_2 , or with the subsequent resubstitution of N₂ for N₂O (Table 1). The mean nadir of arterial Po₂ was 74.5 \pm 8.0 mm Hg.

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<u>Figure 1</u>. Effects of N_2O on regional contractile function (SS) under conditions of constant coronary pressure and HR. Systolic shortening is expressed as a percentage of preischemia values. In the initial ischemia period (N_2) produced with nitrogen, SS is diminished in the LAD ischemic zone but is increased in the adjacent circumflex-perfused control zone. Substitution of 77%–79% N_2O for N_2 (period N_2O) decreased SS in both normal sischemic myocardium. Resubstitution of N_2 (period N_2 ') fully reversed the N_2O -induced depression of contractile function in both zones. Values are mean \pm sp. *Significantly different from values in the same perfusion territory during nitrogen administration (both N_2 and N_2 ').



	N ₂	N ₂ O	N ₂ '
Heart rate (beats/min paced)	112.5 ± 13.4	113.3 ± 12.0	113.3 ± 12.1
MAP (mm Hg)	84.8 ± 19.2	83.9 ± 19.5	81.7 ± 20.7
Coronary pressure (mm Hg)	43.1 ± 8.7	43.3 ± 8.7	43.2 ± 8.7

 $N_2,$ nitrogen; $N_2{\rm O},$ nitrous oxide; $N_2{\rm '},$ second administration of nitrogen; MAP, mean arterial pressure.

"Constant External Stenosis" Experiments

Baseline preischemic SS was 20.9% \pm 3.8% in the LAD-perfused zone and 17.3% \pm 3.2% in the CX-perfused zone.

Left anterior descending coronary artery ischemia decreased SS in the ischemic zone to 68.7% of control values and led to a compensatory increase in SS to 113% of control in the adjacent nonischemic myocardium (Figure 2). Substitution of N_2O for N_2 decreased SS in the hyperdynamic control zone (to 102.9% of control values), similar to the effect found in the constant pressure experiments. Substitution of N_2O also decreased SS in the ischemic zone (to 58.4% of preischemic values, P < 0.05) (Figure 2). However, removal of N_2O did not always lead to reversal of this contractile deterioration. In eight individual cases (Figure 3A, "recovery group") contractile function

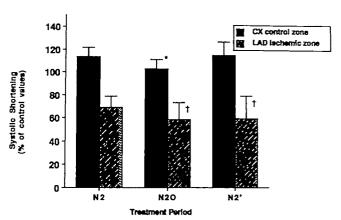


Figure 2. Effects of N_2O on regional contractile function during constant externally applied coronary stenosis. Heart rate and blood pressure were not controlled. In the initial ischemia period (N_2), SS was diminished in the LAD ischemic zone, but increased in the adjacent circumflex-perfused control zone. Substitution of N_2O for N_2 (period N_2O) decreased SS in both normal and ischemic myocardium. However, resubstitution of N_2 for N_2O (period N_2') did not always reverse N_2O -induced deterioration of contractile dysfunction. Values are mean \pm 5D. *Significantly different from values in the circumflex perfusion territory during nitrogen administration. †Different from corresponding LAD values during initial ischemia period (period N_2). See Figure 3 for individual data.

recovered substantially when N_2O was discontinued, but in the five other cases (Figure 3B, "no recovery" group) contractile function deteriorated further when N_2O was discontinued.

When the constant stenosis group is examined as a whole, hemodynamic values did not change significantly (Table 2). Coronary arterial pressure (CAP), transstenotic pressure gradient, heart rate (HR), mean arterial pressure (MAP), and systolic and diastolic arterial pressures were unchanged throughout the experiment. In an effort to account for the progressive deterioration after N2O substitution in 5 of the 13 cases, hemodynamic data were examined separately in this "no recovery" group (Table 2). There was a trend toward initially lower MAP and CAP (period N_2) in the subset of pigs that did not recover after N2O withdrawal, but this trend did not achieve statistical significance (P = 0.06). CAP – left ventricular end-diastolic pressure, an index of coronary perfusion pressure, did not change significantly. The transstenosis pressure gradient (MAP -CAP) was constant in both groups; there was no evidence for collapsing or constricting stenosis. The product of rate and (mean) pressure did not change significantly in the group as a whole or in either subset. Although neither MAP nor HR changed significantly, the MAP/HR index, as described by Buffington (22), decreased to 0.841, a 6% decline over the course of the experiment (Table 2). In this group, the

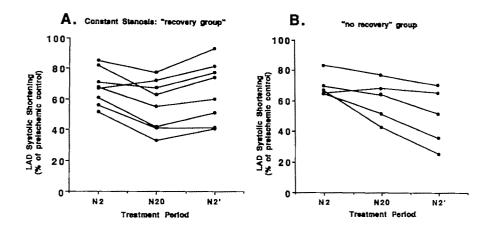


Figure 3. Effects of N_2O on ischemic zone contractile function during constant externally applied coronary stenosis: individual data. In 11 of 13 swine (A and B), N_2O decreased SS in the LAD-perfused myocardium. In eight swine (A: recovery group), SS improved when N_2O was discontinued (period N_2'). In five swine (B: no recovery group), SS deteriorated after N_2O was discontinued.

Table 2. Constant External Coronary Stenosis: Measured and Derived Hemodynamics

	N_2	N_2O	N_2'
HR (beats/min)			
All	77.8 ± 12.2	79.0 ± 12.3	79.4 ± 13.7
No recovery	74.7 ± 8.1	77.1 ± 9.9	81.2 ± 16.6
Recovery	80.0 ± 14.4	80.3 ± 14.1	78.0 ± 13.2
CAP (mm Hg)			
All	37.0 ± 6.7	37.8 ± 6.5	36.7 ± 6.1
No recovery	$32.8 \pm 2.6^{\circ}$	35.1 ± 3.8	32.6 ± 3.2
Recovery	39.6 ± 7.1	39.4 ± 7.5	39.2 ± 6.2
MAP (mm Hg)			
All	72.7 ± 12.2	72.9 ± 12.0	72.9 ± 12.1
No recovery	$66.8 \pm 8.8^{\circ}$	70.0 ± 10.0	67.5 ± 9.0
Recovery	76.3 ± 14.4	74.8 ± 14.1	78.0 ± 13.2
CAP – LVEDP (mm Hg)			
All	28.1 ± 7.7	27.2 ± 6.9	28.0 ± 7.1
No recovery	23.3 ± 4.5	25.0 ± 4.9	24.0 ± 5.7
Recovery	31.1 ± 8.1	28.5 ± 7.8	30.5 ± 7.1
MAP – CAP (mm Hg)			
All	35.7 ± 9.4	35.1 ± 10.2	36.2 ± 10.0
No recovery	34.1 ± 6.9	34.9 ± 7.7	34.9 ± 7.1
Recovery	36.8 ± 11.0	35.3 ± 12.1	37.1 ± 11.9
$MAP \times HR (\times 10^3)$			
All	5.75 ± 1.80	5.87 ± 1.80	5.89 ± 1.82
No recovery	5.05 ± 1.19	5.46 ± 1.46	5.59 ± 1.93
Recovery	6.19 ± 2.05	6.13 ± 2.04	6.09 ± 1.86
MAP/HR ´			
AII	0.939 ± 0.120	0.925 ± 0.100	0.926 ± 0.127
No recovery	0.893 ± 0.053	0.909 ± 0.080	0.841 ± 0.085
Recovery	0.967 ± 0.144	0.935 ± 0.118	0.980 ± 0.123

HR, heart rate; CAP, coronary arterial pressure; MAP, mean arterial pressure; LVEDP, left ventricular end-diastolic pressure.

mean nadir of arterial Po₂ was 83.1 ± 9.3 mm Hg after discontinuation of N₂O.

Discussion

We confirmed that in the constant coronary pressure studies, N₂O decreases contractile performance

slightly both in ischemic myocardium and in the adjacent "normal" myocardium. Nitrous oxide did not induce disproportionate dysfunction in ischemic myocardium when coronary pressure and HR were held constant. In the constant external stenosis studies, when the effects of N_2O on HR, MAP, and coronary stenosis were not controlled, N_2O also worsened contractile performance in both the ische-

Not significantly different from recovery group (P = 0.06). Significantly different from group with recovery after N_2O withdrawal (P = 0.03).

mic myocardium and the adjacent control zone. In these experiments, as in those of Philbin et al. (13), the N_2O -induced deterioration in ischemic zone contractile function was not always reversible. Because contractile function improved upon N_2O withdrawal in the nonischemic zone, the progressive deterioration of contractile function in the ischemic zone of 5 of 13 cases probably represented worsening ischemia in the LAD-perfused myocardium.

Because of our experimental design, hemodynamic measurements were made at the same time as sonomicrometry measurements. It is therefore not possible in the present experiment to establish by post hoc analysis the cause of progressive deterioration in the no recovery group. Several important factors are clear, however. We found no increase in transstenotic pressure gradient suggestive of collapsing or constricting coronary stenosis. Additionally, we found no diffusion hypoxia. It is therefore more probable that the progressive deterioration of contractile function in the no recovery group was hemodynamically mediated. Notably, the MAP/HR ratio decreased significantly in the final N_2 period (-6%, P < 0.05 vs periods N_2 and N_2O). Buffington (22) found that this ratio predicts the degree of myocardial contractile dysfunction during ischemia. Our finding of decreased MAP/HR ratio in the no recovery swine is entirely consistent with the hypothesis that this contractile deterioration was hemodynamically mediated.

On the other hand, it can be argued that "constant" myocardial ischemia is inherently unstable over time and will inevitably progress to myocardial "stunning" or infarction. Although our experimental design required stable dysfunction at the onset, we cannot exclude the possibility that time alone played a role in the progressive deterioration of contractile function found in the no recovery group.

We speculate that the small hemodynamic changes noted in the no recovery group in the final N₂′ measurement period (decreased MAP/HR ratio) either may have been induced by N₂O withdrawal (via lighter anesthesia or decreased sympathetic tone) or may have been simply due to persistent myocardial ischemia. By any measure, however, the hemodynamic changes associated with progressive contractile deterioration in this experiment were small. The conclusion can still be drawn that N₂O administration can initiate progressive deterioration of contractile function, probably ischemic, which is mediated by small changes or by initial differences in hemodynamic parameters.

Our results are in agreement with the study of Nathan (14), which indicated that 50% N₂O induces

myocardial ischemia by its hemodynamic effects rather than by a unique toxicity to ischemic or nearischemic myocardium. Our study is distinguished from that of Nathan in that we administered a higher concentration of N_2O (75%–78% in our study vs 50%) in Nathan's study) in the test period, and have therefore more fully tested N₂O's potential to induce myocardial dysfunction. Furthermore, we studied the addition of N₂O to a barbiturate/narcotic anesthetic base, so this study mimics the clinical situation in which N₂O is added to basal anesthesia in order to increase anesthetic depth. This study design has the advantage that it measures the absolute effects of N₂O and does not measure the possibly confounding effects of the simultaneous withdrawal of another negative inotropic anesthetic, as in the studies of Nathan (14, 15). It must be recognized, however, that some of the measured effects of N₂O in the current study could be related to unmeasured neural or humoral effects of deeper anesthesia, which would not be detected by our hemodynamic measurements.

The results of our study stand in contrast to those of Leone et al. (23), who found that N_2O , 40%–60% inspired, when added to a fentanyl anesthetic in dogs with critical coronary stenosis, caused regional dysfunction only in the jeopardized zone and not in adjacent normal tissue. The dysfunction found by Leone et al. was very mild, however—evident only as postsystolic shortening, not as diminished SS. The differences in results between our study and those of Leone et al. are probably accounted for by differences in the initial degree of ischemia. The baseline ischemic dysfunction caused by coronary stenosis in our study (SS decreased to 64%–68% of control values) was more severe than the initial dysfunction caused by the "critical" stenosis in Leone's study (SS% decreased only to 83% of control values, P = NS vs their control period). Because the initial ischemic insult was greater in our study, the compensatory hyperdynamic response was greater in the adjacent normal myocardium. This may explain why we saw a greater depression of contractile performance in the control zone: the baseline performance was increased more than in the study by Leone et al. Another point of contrast between these two studies is that Leone et al. found the dysfunction induced by N₂O to be fully reversible, whereas we found, as did Philbin et al. (13), that this was not always true. This finding is probably also accounted for by the greater initial ischemia in our current study and in that of Philbin et

The results of the present study are also in contrast to those of Coetzee and associates (24), who found that N₂O, when added to a halothane anesthetic, did

not diminish contractility in nonischemic swine myocardium. Although Coetzee et al. used a sensitive measure of contractility, the end-systolic pressure-length relationship (25), no significant negative inotropic effect of N_2O was found at concentrations of 30%, 50%, or 70%. Differences between our results and those of Coetzee et al. are probably accounted for by the fact that the latter studied the additive effects of N_2O on myocardial contractility when N_2O was superimposed upon a halothane (0.5%)/fentanyl/pancuronium anesthetic. The mild negative inotropic effects of N_2O may have been partially obscured because of the presence, in that study, of another more potent negative inotropic drug, halothane.

The current study has several advantages over prior studies, and a few limitations, that must be discussed.

First, we used a swine model of acute myocardial ischemia, which is preferable to the dog model used in other studies (14,15,23) because swine have a very limited coronary collateral circulation (26). In dogs, acute drug-induced changes in collateral flow can significantly affect the severity of ischemia (27). In acute ischemia studies, a model lacking in collateral flow should therefore be used, or the effects of the experimental intervention on collateral flow should be accounted for. Our study has the advantage of using an animal model of acute ischemia essentially lacking in collateral coronary flow.

Second, because we tested the physiologic effects of higher concentrations of N_2O than were tested in some prior studies (14,15,24), we are more certain of the potential effects of N_2O used in clinically useful concentrations.

Third, in our constant external stenosis experiments, we used a model in which direct effects of N_2O at the stenosis site (such as passive pressure-induced collapse) could potentially be observed. We did not, however, specifically test the ability of the free arterial wall within the stenosis to actively constrict in this study, and therefore do not have a "positive control."

One obvious disadvantage of our preparation is that it required dissection of the LAD coronary artery in order to apply the experimental instrumentation. Dissection of the proximal LAD interrupts the adrenergic innervation and might well have prohibited our finding any neurally mediated effects of N₂O at the stenosis site.

A final potential disadvantage of this study is that myocardial blood flow was not directly measured, so the effects of N_2O on the intramyocardial distribution of blood flow could not be quantified. Although the use of radioactive microspheres would have provided

additional useful information about the effects of N₂O in acute myocardial ischemia, we intentionally chose not to use this technique because of the possible attendant problem of injection of air microbubbles along with the microspheres, and the theoretical possibility that embolized microbubbles could be expanded by N₂O. Radioactive microspheres are normally agitated or sonicated vigorously in the presence of an air bubble as an aid to mixing (28). Preparation of a microsphere injection is thus similar to preparation of a sample for injection of microbubbles for contrast echocardiography (29). The injection of such microbubbles into the circulation, however, can lead to transient myocardial dysfunction (29), and the rate of clearance of the microbubbles is not well established. If microbubbles remain entrapped in the coronary circulation because of a microsphere injection, N₂O could expand the retained bubbles and cause worsening ischemia due to its effect on the size of gas bubbles, rather than observable hemodynamic effects or direct toxicity. Although more information about the coronary flow distribution would have been desirable in this experiment, we felt it most important to exclude the possibility that any contractile deterioration could be caused by microbubbles expanded by N₂O, so we did not use the microsphere

In summary, we found that N₂O decreases contractile function in both ischemic myocardium and in the adjacent nonischemic myocardium. When HR and coronary pressure are very tightly controlled, N₂O has no disproportionate effect on ischemic myocardium. In clinical practice, however, such tight control of HR is very difficult, and coronary pressure can be controlled only indirectly, by maintaining a constant aortic pressure. In the setting of acute ischemia, small variations in HR and blood pressure due to the effects of N₂O administration can worsen ischemic myocardial contractile dysfunction. This N₂Oinduced, hemodynamically mediated deterioration is often not reversible by the simple measure of discontinuing N2O. Nitrous oxide should therefore continue to be used, as should all anesthetic drugs with cardiovascular side effects, with caution in patients with coronary artery disease and possible myocardial ischemia.

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Droperidol Prevents Serotonin-Induced Bronchospasm in the Guinea Pig

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GENTIL B, MACQUIN-MAVIER I, LIENHART A, HARF A. Droperidol prevents serotonin-induced bronchospasm in the guinea pig. Anesth Analg 1991;72:612–5.

The effects of droperidol on bronchoconstriction induced by serotonin (5-HT) were studied in mechanically ventilated, paralyzed guinea pigs that had been anesthetized with pentobarbital. Droperidol did not modify the resting bronchial tone but prevented the bronchoconstrictor effects of 5-HT in a dose-related manner. Pretreatment with propranolol, hexamethonium, or prazosin did not alter the protec-

tive effects of droperidol on 5-HT-induced bronchoconstriction. The bronchoconstrictor responses to histamine or acetylcholine were not affected by droperidol. These results suggest that the protective effects of droperidol on 5-HTinduced bronchoconstriction are mediated through 5-HT receptor blockade on bronchial smooth muscle.

Key Words: ANESTHETICS, INTRAVENOUS—droperidol. LUNGS, BRONCHOSPASM—pulmonary resistance. RECEPTORS, SEROTONIN (5- HT_2). SEROTONIN, BRONCHOSPASM.

Neuroleptic drugs are known to block dopamine receptors, the major mechanism involved in their antipsychotic action. It has also been shown that some neuroleptics (spiroperidol, buspirone) are able to bind to serotonin (5-HT) receptors (1). With the use of a large number of potent and selective antagonists, binding to the 5-HT₂ class of binding sites has been demonstrated in studies on brain tissue for spiroperidol (2,3) and several other neuroleptics (4,5).

One in vitro study (6) has shown the antagonist properties of neuroleptics such as trifluoperazine on peripheral 5-HT₂ receptors in the trachea. Recent in vitro studies (7,8) suggest that airway 5-HT₂ receptor activation induces bronchoconstriction. In keeping with this finding is the decrease in bronchoconstriction observed after injection of ketanserin, a known 5-HT₂ antagonistic, in experimental endotoxemia (9,10), in pulmonary embolism (11), and in chronic obstructive pulmonary disease (12).

To our knowledge, no study has assessed the peripheral antiserotoninergic activity of neuroleptic agents in vivo. In this study, we evaluated the effects of droperidol, one of the major tranquilizers used in anesthesia, on 5-HT-induced bronchoconstriction in the guinea pig.

Methods

This study was performed according to institutional guidelines for animal experimentation. Male Hartley guinea pigs (Charles River, France) weighing 300 ± 20 g were anesthetized with 37 mg/kg pentobarbital intraperitoneally and both jugular veins were cannulated. After tracheotomy, 0.1 mg/kg vecuronium bromide was administered intravenously every 30 min throughout the experiment to block respiratory efforts, and mechanical ventilation with a ventilator delivering a constant inspiratory flow was initiated. Respiratory frequency and tidal volume were 60 cycles/min and 6 mL/kg. Body temperature was monitored and maintained at 38°C using a thermostatically controlled heated pad. Intratracheal airway pressure was measured with a Validyne MP45 ± 50 cm H₂O transducer connected to a side hole in the tracheal cannula. Inspiratory flow was measured with a heated Fleisch No. 000 pneumotachograph and a Validyne MP45 \pm 2 cm H₂O transducer. Tidal volume was calculated by integration of the inspira-

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tory flow. Tracheal pressure, inspiratory flow, and tidal volume signals were digitized and fed into a microcomputer. Respiratory conductance (the reciprocal of resistance) was computed at each breath, as previously described (13), and the mean value obtained for every 30-s set of measurements was displayed. A period of 30 min was allowed to elapse before the beginning of the study.

Droperidol and 5-HT-Induced Bronchospasm

In a group of eight guinea pigs, five sequential bronchospasms were provoked at 10-min intervals with 5-HT, administered intravenously as a 3-min infusion at a rate of 100 ng·kg⁻¹·s⁻¹. The reproducibility of 5-HT-induced bronchospasms under our experimental conditions has been demonstrated in a previous study (14). The first bronchospasm was preceded by saline injection (control bronchospasm), and the following ones were preceded by incremental doses of droperidol administered intravenously at doses of 0.001, 0.01, 0.1, and 1 mg/kg, respectively. Doses of droperidol are expressed as cumulative doses.

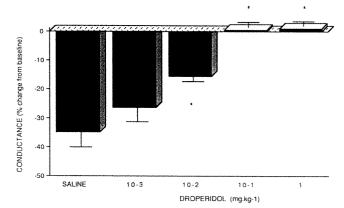
Three additional groups of six guinea pigs each were studied to evaluate the influence of the autonomic nervous system on the interaction between 5-HT and droperidol. Animals were treated intravenously with either propranolol (5 mg/kg), hexamethonium (5 mg/kg), or prazosin (0.3 mg/kg) 10 min before the 5-HT infusion (100 ng·kg⁻¹·s⁻¹). When respiratory conductance had returned to control values, 1 mg/kg droperidol was injected and guinea pigs were challenged with 5-HT again 10 min later.

Droperidol and Bronchospasm Induced by Histamine or Acetylcholine

Two groups of six guinea pigs each were challenged by histamine or acetylcholine. After injection of saline, a first bronchospasm was provoked 10 min later by a 3-min infusion of either histamine (100 ng·kg⁻¹·s⁻¹) or acetylcholine (500 ng·kg⁻¹·s⁻¹). When respiratory conductance had returned to control values, 1 mg/kg droperidol was injected and the guinea pigs were challenged again with histamine or acetylcholine 10 min later.

Analysis of Results

The results are expressed as mean \pm SEM. Data were analyzed by repeated-measures analysis of variance



<u>Figure 1</u>. Effect of incremental doses of droperidol on sequential serotonin-induced bronchospasms. Droperidol was administered before infusion of 5-HT and dose-dependently prevented bronchospasm. Values are expressed as mean ± SEM. *Asterisks* denote a significant change from control value.

and two-by-two comparisons were made by Scheffe's t-test. P < 0.05 was considered to be significant.

Results

Changes in respiratory conductance during bronchoconstriction are expressed as percentage decrease from control value recorded just before infusion of the provocative agent.

Droperidol and 5-HT-Induced Bronchospasm

Droperidol injection did not significantly change the baseline respiratory conductance, which was 27.6 \pm 1.0 mL·kPa⁻¹·s⁻¹ after saline and 27.8 \pm 0.9, 28.5 \pm 0.9, 28.1 \pm 0.7, and 28.6 \pm 1.0 mL·kPa⁻¹·s⁻¹ after each of the four doses of droperidol.

5-HT administered at a rate of $100 \text{ ng} \cdot \text{kg}^{-1} \cdot \text{s}^{-1}$ decreased the conductance by $34.9\% \pm 6.0\%$. Droperidol dose-dependently prevented 5-HT-induced bronchoconstriction. This attenuation was found significant (P < 0.001) after 0.01 mg/kg droperidol: the decrease in conductance was $15.5\% \pm 2.7\%$. Higher doses of droperidol fully prevented 5-HT-induced bronchospasm (Figure 1).

Pretreatments with propranolol, hexamethonium, or prazosin did not alter the prevention of 5-HT-induced bronchoconstriction by 1 mg/kg droperidol (Figure 2).

Effects of Droperidol on Histamine- and Acetylcholine-Induced Bronchospasm

Droperidol did not affect histamine-induced bronchoconstriction. Decreases in conductance were re-

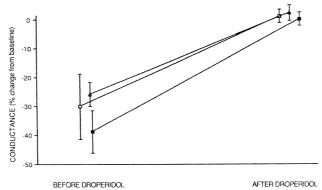


Figure 2. Effect of 1 mg/kg droperidol on serotonin-induced bronchospasm in three groups of guinea pigs pretreated with 5 mg/kg hexamethonium (———), 0.3 mg/kg prazosin (——), or 5 mg/kg propranolol (———). Values are expressed as mean \pm sem.

spectively $15.1\% \pm 7.9\%$ before 1 mg/kg droperidol and $15.7\% \pm 4.9\%$ after droperidol (not a significant difference).

Similar results were observed concerning the effects of droperidol on acetylcholine-induced bronchospasm: the decrease in respiratory conductance was $35.9\% \pm 8.3\%$ before droperidol and $46.3\% \pm 3.4\%$ after droperidol (not a significant difference).

Discussion

Our results demonstrate that droperidol prevents the bronchospasm caused by 5-HT in the guinea pig. This effect on the airway narrowing produced by 5-HT could be ascribed to a droperidol-induced change in autonomic nervous system activity, or to an interaction of droperidol with 5-HT at the level of the smooth muscle receptors of the airways. Because droperidol injection did not significantly modify either histamine or acetylcholine-induced bronchospasm, it is therefore unlikely that a nonspecific effect of droperidol explains our results.

Autonomic nervous system activity is one of the major determinants of bronchial tone, and the interaction of droperidol with this system might have explained our results. Droperidol is considered to be devoid of anticholinergic activity (15). On the other hand, droperidol decreases α -sympathetic activity and increases blood catecholamine levels (16). Droperidol intravenously injected in intubated patients decreases tracheal tone obtained from measurements of the cuff pressure (17), an effect attributed to a decrease in α -adrenergic activity. However, in our study pretreatment with α_1 -adrenergic blocker did not alter the protective effects of droperidol on 5-HT-induced bronchoconstriction.

Another explanation for the prevention that was observed could be the increase in catecholamine levels. We demonstrated that propranolol pretreatment failed to inhibit the protective effects of droperidol on bronchospasm, indicating that increased β -adrenergic activity due to droperidol cannot explain our results. In fact, although droperidol increases release of catecholamines from the adrenal medullary cells in vitro (18), droperidol administration is associated with only transient increases in plasma norepinephrine concentrations, while plasma epinephrine concentrations remain unchanged (16).

Besides the classical pathways of the autonomic nervous system, a nonadrenergic inhibitory system exists in the respiratory system that is reflexly activated by infused 5-HT (19). This nonadrenergic inhibitory system pathway includes a synapse between vagal preganglionic fibers and specific postganglionic neurons and so is blocked by, for example, the ganglionic blocker hexamethonium (19). We found that hexamethonium pretreatment had no effect on the droperidol-induced prevention of bronchospasm, indicating that a modulation of the nonadrenergic inhibitory system by droperidol cannot explain our observation.

Interaction between 5-HT receptors on bronchial smooth muscle and droperidol is likely to be an explanation for our results. Although neuroleptic agents are known from in vitro studies to bind to 5-HT receptors, their activity on peripheral 5-HT receptors has not been studied in vivo. The neuroleptic trifluoperazine was shown to inhibit tracheal smooth muscle contraction induced in vitro by 5-HT (6). The receptor involved in the contraction is the 5-HT₂ subtype as shown by the use of specific antagonists like ketanserin, whereas other 5-HT subtypes seem not to be involved (7,8,20). In the present study, the prevention of bronchoconstriction by 1 mg/kg droperidol was found to be independent of autonomic nervous system activity and specific of 5-HT, and strongly suggests competitive antagonism of droperidol at 5-HT₂ receptors.

The range of doses of droperidol (0.01–1 mg/kg), which significantly decreased 5-HT-induced bronchospasm, was found to be similar to those previously recommended for the anesthesia in guinea pigs (21). Because of interspecies differences, droperidol–5-HT interaction on human bronchial smooth muscle remains to be established in vivo. The role of 5-HT in regulation of airway tone is still unclear (22), although 5-HT increases airway resistance (23) and is involved in the clinical manifestations, including bronchoconstriction, seen in patients with carcinoid tumors (24). On the other hand, a beneficial effect on

airway resistance was found after ketanserin (a 5-HT $_2$ antagonist) administration in pathological conditions in which bronchial tone is increased (12). Further clinical studies are needed to investigate the effects of droperidol administration on airway resistance in similar circumstances.

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Comparison of Intravenous Sedative-Analgesic Techniques for Outpatient Immersion Lithotripsy

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MONK TG, BOURÉ B, WHITE PF, MERETYK S, CLAYMAN RV. Comparison of intravenous sedative-analgesic techniques for outpatient immersion lithotripsy. Anesth Analg 1991;72:616–21.

Fifty-three unpremedicated outpatients undergoing elective extracorporeal shock wave lithotripsy using an unmodified Dornier HM-3 lithotriptor received one of two different intravenous sedation-analgesia techniques. Both intravenous midazolam-alfentanil and fentanyl-propofol techniques produced conditions comparable to those achieved with epidural anesthesia during immersion lithotripsy. Of the two sedative-analgesic techniques, midazolam-alfentanil was associated with greater intraoperative amnesia (81% vs

38%), whereas fentanyl-propofol produced less cardiorespiratory depression and fewer postoperative side effects (e.g., pruritus). Compared with a standard epidural anesthesia technique, the mean anesthesia and recovery times were significantly shorter with the two intravenous sedationanalgesia techniques (57–62 min vs 105 min and 143–147 min vs 199 min, respectively). These data suggest that combinations of either midazolam and alfentanil or fentanyl and propofol are viable alternatives to epidural anesthesia for outpatient immersion lithotripsy.

Key Words: ANALGESICS, FENTANYL.

ANESTHETIC TECHNIQUES, EPIDURAL—lithotripsy.

ANESTHETICS, INTRAVENOUS—proposol, fentanyl.

sedative-hypnotic and analgesic drugs remains the

most widely used technique for improving patient

comfort during these procedures (6,7). However, excessive doses of these drugs can produce signifi-

cant respiratory depression (8). Use of continuous IV

infusions of short-acting anesthetic and analgesic

drugs has been found to be associated with fewer

intraoperative side effects and shorter recovery times

than traditional intermittent bolus techniques (9,10).

Infusions of sedative-hypnotic drugs have also been

used to provide a stable level of sedation during local

Extracorporeal shock wave lithotripsy (ESWL) is a noninvasive procedure for the treatment of calculi located in the upper urinary tract (1). The discomfort associated with immersion shock wave therapy when using the unmodified Dornier HM-3 lithotriptor has necessitated the use of general or regional anesthesia (1,2). Continuous lumbar epidural anesthesia is the most commonly used anesthetic technique because it offers the possibility of titrating the local anesthetic to meet the needs of the individual patient without the logistical difficulties associated with general anesthesia in this setting. Nevertheless, achieving adequate analgesia and positioning the patient for the ESWL procedure can be a time-consuming process with epidural anesthesia. Recovery can also be prolonged as a result of residual sympathetic blockade (3).

Inadequate analgesia during ESWL procedures necessitates the use of lower shock wave pressures, thereby increasing the requirement for retreatment (4–6). Intermittent bolus injection of intravenous (IV)

We designed a study to compare the clinical efficacy of two different sedative-analgesic techniques with respect to their ability to produce a stable level of sedation and analgesia without cardiopulmonary de-

sion lithotripsy procedure has not been evaluated.

and regional anesthesia (11,12).

Recently, investigators have described the use of an alfentanil infusion to provide sedation and analgesia in patients undergoing ESWL therapy for gallstones (13,14). The availability of lithotriptor devices that utilize lower energy levels has facilitated the use of monitored anesthesia care techniques (15,16). Yet the effectiveness of supplemental IV sedative-analgesic techniques, as an alternative to epidural (and general) anesthesia, for the more painful immer-

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pression. In addition, we assessed the amnestic properties, recovery times, and postoperative side effect profiles of the two sedative-analgesic techniques. Recovery times and outcome data with these techniques were compared with those associated with epidural anesthesia at our institution.

Materials and Methods

Fifty-three unpremedicated, consenting adult outpatients, ASA physical status I-III, undergoing elective ESWL for upper urinary tract calculi using an unmodified Dornier HM-3 lithotriptor were studied according to a protocol approved by the Washington University Human Studies Committee. After obtaining written informed consent, these patients were randomly assigned to receive either a fentanyl-propofol (FP) or a midazolam-alfentanil (MA) technique according to an open-parallel protocol design. Exclusion criteria included age less than 18 yr, history of drug or alcohol abuse, or an allergic reaction to one of the study medications. With the exception of the anesthesiologist, all patient assessments were performed by individuals who were blinded as to the sedation-analgesic technique used during the lithotripsy procedure.

After a routine preoperative evaluation, baseline measurements of mean arterial pressure, heart rate, respiratory rate (RR), and room air oxygen saturation (Sao₂) were obtained with a Dinamap automatic blood pressure cuff, electrocardiogram, and Datex capnograph-pulse oximeter, respectively. After placement of the IV catheter, 1.5 μ g/kg IV fentanyl (FP group) or 0.05 mg/kg IV midazolam (MA group) was administered in the preoperative holding area. Patients were allowed to position themselves in the lithotriptor chair, and supplemental oxygen, 4 L/min, was administered using nasal prongs containing a sampling port for determining RR by monitoring end-tidal carbon dioxide concentration.

After placement of the patient in the warm-water (37°C) immersion tank (approximately 10–15 min after the initial doses of premedication), additional fentanyl (1.5 μ g/kg IV, FP group) or midazolam (0.05 mg/kg IV, MA group) was administered. Patients were then given one of two maintenance drugs. Group 1 (FP, n=26) received a loading dose of 0.5 mg/kg IV propofol followed by an initial maintenance infusion rate of 50 μ g·kg⁻¹·min⁻¹. Group 2 (MA, n=27) received a loading dose of 10 μ g/kg IV alfentanil and an initial maintenance infusion rate of 1.0 μ g·kg⁻¹·min⁻¹. The subsequent maintenance infusion rates were varied to maintain an adequate

sedative-analgesic state (i.e., calm and comfortable) using either a Baxter model AS20GH (propofol) or a Bard Harvard Mini-infuser 900 (alfentanil) syringe pump. Mean arterial pressure, heart rate, RR, and Sao_2 were recorded in the preoperative holding area, after the loading dose, 2 and 5 min after initiating the maintenance infusion, and then every 5 min until the end of the ESWL procedure. Intraoperative side effects including episodes of patient movement, spontaneous complaints of pain, and oxygen desaturation ($Sao_2 < 90\%$) were also recorded. The anesthesia time was defined as the time from administration of the premedication in the preoperative holding area until arrival in the postanesthesia care unit (PACU).

The degree of sedation and analgesia was assessed at 5-min intervals and was considered adequate if the patient was calm and comfortable (i.e., no spontaneous complaints of pain, movements, or facial grimaces in response to the shock waves). In response to bradypnea (i.e., RR < 10 breaths/min) or oxygen desaturation ($Sao_2 < 90\%$), the maintenance infusion rate was decreased or transiently discontinued. The infusion was restarted at a lower infusion rate when the Sao_2 increased above 90% with an RR > 8 breaths/min. At the end of the procedure, the maintenance infusions were discontinued and the urologist was asked to evaluate the adequacy of the patient's intraoperative sedation and analgesia using a four-point scale (1 = inadequate, 2 = fair, 3 = good,4 = excellent). The anesthesiologist monitoring the patient was also asked to evaluate independently the adequacy of the sedation technique using the same four-point scale.

The patients were then transported to the PACU where they were observed until they were judged to be suitable for discharge by the nursing staff according to standardized criteria. Immediately before discharge from the PACU, patients were asked to assess their satisfaction with the sedative-analgesic technique and to quantitate their level of comfort during the procedure using a 100-mm visual analog scale (0 = extremely uncomfortable to 100 = extremely)comfortable). The PACU nurse was also asked to evaluate the adequacy of patient recovery using the previously described four-point scale. In addition, the need for analgesic, antiemetic, and/or sedative medication in the PACU was recorded, as well as the time to transfer from phase 1 (lying on the gurney) to phase 2 (sitting up in a chair) recovery and discharge time (phase 1 and phase 2). Variables related to the urologic procedure itself were also recorded (e.g., stone size, density and location, number of shocks delivered, maximal voltage [kV], and degree of fragmentation). The following day, patients were ques-

Table 1. Demographic Characteristics of the Patients and the Extracorporeal Shock Wave Lithotripsy Variables in the Two Treatment Groups

	Fentanyl-propofol	Midazolam-alfentanil
Number (n)	26	27
Sex (M/F)	18/8	18/9
Age (yr)	53 ± 10	47 ± 14
Height (cm)	172 ± 10	173 ± 9
Weight (kg)	84 ± 18	81 ± 13
Stone size (mm²)	81 ± 50	73 ± 89
Stone location (%)		
Upper calyx	8	15
Medial calyx	8	11
Lower calyx	27	26
Renal pelvis	30	22
Ureter	27	26
Stone density (%)*		
1	0	0
2	10	9
2 3	19	26
4	<i>7</i> 1	65
Number of shocks	2172 ± 601	2000 ± 793
Voltage (kV)	21.4 ± 1.0	21.1 ± 1.0
Fragmentation (%)		
<5 mm	90	89
≥5 mm	10	0
Undefinable	0	11

Values for age, height, weight, stone size, number of shocks, and voltage are expressed as mean ± sp.

"I = radiolucent to 4 = very opaque.

tioned regarding their recall of events during the procedure and the occurrence of any side effects after discharge.

Data analysis. Data were analyzed with the Stata statistical program using one-way analysis of variance with the Bonferroni option to compare continuous demographic data, cardiorespiratory variables, anesthesia time, lithotripsy room stay, ESWL time, phase 1 and 2 recovery times, pain scores, and stone-related data for the two sedative-analgesic treatment groups. Nominal data were analyzed using χ^2 analysis. Differences were considered to be statistically significant when the *P* value was <0.05. Values are expressed as mean ± standard deviation (unless otherwise specified).

Results

The two IV sedation-analgesia groups were comparable with respect to demographic data (Table 1). Calculi locations, densities, and sizes were also comparable in both treatment groups. In addition, the stone fragmentation results were comparable in both groups after the procedure. Time in the lithotriptor

Table 2. Duration of Key Perioperative Events

	Fentanyl- propofol	Midazolam- alfentanil
Anesthesia time	62 ± 19	57 ± 19
ESWL procedure time	35 ± 14	32 ± 16
ESWL room time	61 ± 15	55 ± 16
Phase 1 recovery (PACU)	41 ± 16	51 ± 25
Discharge (phases 1 and 2)	147 ± 51	$143.\pm 56$

ESWL, extracorporeal shock wave lithotripsy; PACU, postanesthesia care unit. Values are expressed as mean ± sp minutes.

room ("room time") did not differ between the two treatment groups. Similarly, anesthesia, procedure, recovery, and discharge times did not significantly differ between the two IV sedation-analgesia groups (Table 2).

The sedative and analgesic dosage requirements (and ranges) for the MA group were 7.3 ± 1.9 mg (5-11 mg) midazolam and $4.4 \pm 1.8 \text{ mg}$ (2.2-9.0 mg)alfentanil. The total drug dosages for the FP group were 226 \pm 85 μ g (100–400 μ g) fentanyl and 277 \pm 105 mg (113–556 mg) propofol. Changes in the hemodynamic variables are summarized in Figures 1A and 1B. A more rapid initial decline in mean arterial pressure was noted at the start of the sedation period in the MA group; however, subsequently there were no hemodynamic differences between the two IV sedation-analgesia treatment groups. Heart rate remained stable and values were comparable in both sedation-analgesia groups. As expected, the MA group had slower RRs and lower Sao₂ values (Figures 2A and 2B).

Patient, anesthesiologist, urologist, and PACU nurse satisfaction with the two sedation techniques are summarized in Table 3. Both techniques were judged to be good or excellent in more than 90% of the cases by the patients and the health-care personnel. No patient required general or regional anesthesia to complete the ESWL procedure, and no case had to be prematurely terminated because of inadequate sedation or analgesia.

Perioperative side effects are summarized in Tables 4 and 5. Patients in both groups were comfortable during the procedure and had a low incidence of movement in response to the shock wave treatment. The number of episodes of oxygen desaturation (Sao₂) < 90%) was significantly higher in the opioid infusion (MA) group. Interestingly, the incidence of pain or discomfort on the first postoperative day was also higher in the MA group (78% vs 50% FP, P < 0.05). Recall of specific intraoperative events was significantly less frequent in the MA group, whereas itching was more common (15% vs 0% FP, P < 0.05).

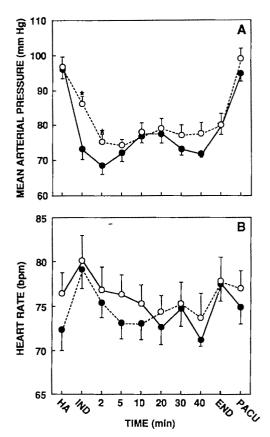


Figure 1. A, Perioperative mean arterial blood pressures in patients receiving either fentanyl-propofol (FP), n=26 (——), or midazolam-alfentanil (MA), n=27 (——). B, Heart rate values in patients receiving either fentanyl-propofol (FP), n=26 (——) or midazolam-alfentanil (MA), n=27 (——). Mean values \pm SEM, *P<0.05 was considered to be statistically significant. HA, in preoperative holding area; IND, after the loading dose; END, at end of the ESWL procedure; PACU, in postanesthesia care unit.

Incidences of nausea, confusion, and excessive sedation were similar in both groups during the first 24 h after the procedure. The postoperative patient assessment questionnaire revealed that both sedation-analgesia techniques were highly acceptable to the patients (Table 5).

Discussion

Simplified anesthetic techniques are desirable if they can be rapidly performed without compromising patient safety and comfort, or requiring modification of the surgical technique. Both IV sedative-analgesic techniques that we evaluated appear to be highly effective and efficient alternatives to the standard epidural anesthetic technique for immersion ESWL procedures. The major advantage of these sedative-analgesic infusion techniques over epidural anesthesia for ESWL procedures is related to significantly

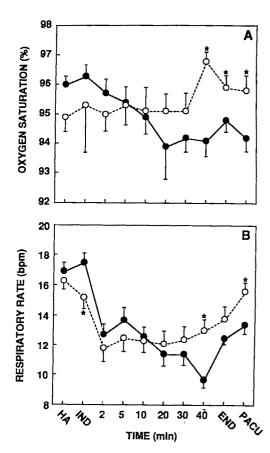


Figure 2. A, Oxygen saturation values in patients receiving either fentanyl-propofol (FP), n=26 (—O—) or midazolam-alfentanil (MA), n=27 (—O—). Mean values \pm sem, $^*P < 0.05$ was considered to be statistically significant. B, Perioperative respiratory rates in patients receiving either fentanyl-propofol (FP), n=26 (—O—) or midazolam-alfentanil (MA), n=27 (—O—). HA, in preoperative holding area; IND, after the loading dose; END, at end of the ESWL procedure; PACU, in postanesthesia care unit.

shorter preparation and recovery times. In addition, patients were able to position themselves in the lithotriptor chair and retain bladder function, thereby eliminating the need for intraoperative bladder catheterization.

When we compared our most recent experience with lidocaine epidural anesthesia for lithotripsy to these two sedation-analgesic techniques (unreported data), we found that the anesthesia (105 ± 35 min), phase 1 recovery (109 ± 43 min), and discharge (199 ± 64 min) times were all significantly longer with the epidural technique (mean values \pm sp). In addition, our findings revealed that a higher percentage of patients had to be hospitalized for at least 23 h after lithotripsy because of side effects or prolonged recovery after the regional block technique (10% vs 0% with the IV techniques). Our incidence of unanticipated hospital admissions with epidural anesthesia was identical to the incidence reported at the Mason

<u>Table 3</u>. Assessment of Adequacy of the Fentanyl-Propofol and Midazolam-Alfentanil Techniques by the Patient and the Professional Staff

	Pai	tient	Uro	logist	Anesth	esiologist	PACU	J nurse
Scale	FP	MA	FP	MA	FP	MA	FP	MA
Excellent	92	78	96	89	63	68	79	84
Good	8	22	4	11	33	24	21	12
air	0	0	0	0	4	8	0	4
nadequate	0	0	0	0	0	0	0	0

FP, fentanyl-propofol; MA, midazolam-alfentanil; PACU, postanesthesia care unit.

<u>Table 4</u>. Intraoperative Side Effects in the Two Sedative-Analgesic Groups

	Fentanyl-propofol		Midazolam- alfentanil	
	No. patients	No. episodes	No. patients	No. episodes
Disruptive movements	10	16	14	22
Spontaneous complaints of pain	17	23	13	18
Oxygen saturation <90%	6	7	13 ^a	22 ^a

[&]quot;Significantly different from the fentanyl-propofol group, P < 0.05.

<u>Table 5</u>. Postoperative Patient Assessment at the Time of Discharge From the Recovery Room

	Fentanyl- propofol	Midazolam- alfentanil
Recall of events during the procedures (%)	62	19ª
Itching during and after the procedure (%)	0	15 ^a
Comfort analog score $(0 = minimal to 100 = maximal)^b$	94 ± 11	93 ± 12
Patients desiring same sedative- analgesic technique (%)	96	100
Patients would feel less worried about future ESWL (%)	85	59
Patients without any postoperative complaints (%)	96	96

ESWL, extracorporeal shock wave lithotripsy

Clinic in Seattle, Washington, for patients receiving chloroprocaine and lidocaine epidural anesthesia for outpatient lithotripsy (3). Thus, it would appear that the use of continuous IV infusion of rapid and short-acting sedative (propofol) or analgesic (alfentanil) drugs can offer significant advantages over regional anesthesia in the outpatient setting.

Although minor differences were noted between the two sedative-analgesic groups, hemodynamic and respiratory changes were acceptable with both techniques. There was a greater decrease in the mean arterial pressure immediately after the loading dose of alfentanil in the midazolam-pretreated group (MA). The use of benzodiazepine-opioid combinations may also predispose the patient to hypoxemia and apnea (17). Even though mean respiratory rates were initially higher in the MA (vs FP) group, those patients had a greater incidence of transient oxygen desaturation (<90%) and ended the procedure with lower RR values.

Overall, the patients (as well as their health-care providers) were highly satisfied with both IV sedation-analgesia techniques. In fact, almost all patients would choose the same technique for a future ESWL procedure. Although the MA group experienced a higher incidence of postoperative itching, this combination did result in better intraoperative amnesia. A high incidence of amnesia and pruritus is expected when using a benzodiazepine-opioid combination. The requirement for antiemetic therapy in the PACU was similar in both sedative-analgesic groups (4%–11%) and compared favorably with our recent experience with epidural anesthesia (5%).

Techniques involving the use of local anesthetic infiltration or application of a topical cream (eutectic mixture of local anesthetics, EMLA, Astra Pharmaceutical Products, Inc., Westborough, Mass.) have also been employed as alternatives to general and regional anesthesia (18–21). Unfortunately, infiltration techniques are time-consuming and have necessitated the use of reduced shock wave energy (14–16 kV). Further studies are needed to compare the cost-efficiency and patient acceptance of these local anesthetic techniques versus the use of IV sedative-analgesic techniques. It is possible that a combination of local anesthesia and IV sedation may have advantages over either technique alone.

In conclusion, the use of IV sedative-analgesic techniques proved to be both safe and effective for monitored anesthesia care in outpatients undergoing immersion lithotripsy. Both techniques allowed full

a Significantly different from the fentanyl-propofol group, P < 0.05.

^bValues here are expressed as mean \pm 5D.

shock wave energy (20 kV) to be maintained throughout the procedure. The combination of fentanyl and propofol appears to be superior to midazolamalfentanil with respect to intraoperative respiratory stability and postoperative side effects. However, the midazolam-alfentanil combination provided more effective intraoperative amnesia. The use of intravenous sedation-analgesia techniques would appear to offer advantages over epidural anesthesia techniques with respect to shorter anesthesia preparation and recovery times for these ambulatory procedures.

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Contribution of the Lungs to the Clearance of Exogenous Dopamine in Humans

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SUMIKAWA K, HAYASHI Y, YAMATODANI A, YOSHIYA I. Contribution of the lungs to the clearance of exogenous dopamine in humans. Anesth Analg 1991;72: 622–6.

The contribution of the lungs to the clearance of exogenous dopamine was analyzed in humans by measuring plasma pulmonary concentrations of dopamine and the pulmonary plasma flow before and after infusion of dopamine. Contribution of the lungs was defined as the ratio between clearance by the lungs and the total plasma clearance of dopamine. Significant transpulmonary gradient of plasma

dopamine was observed with infusions at rates of 1.0 and 2.0 $\mu g \cdot k g^{-1} \cdot min^{-1}$, but not at 0.5 $\mu g \cdot k g^{-1} \cdot min^{-1}$. The calculated contribution values were 4.90%, 19.23%, and 20.60% at the doses of 0.5, 1.0, and 2.0 $\mu g \cdot k g^{-1} \cdot min^{-1}$, respectively. The results suggest that the clearance mechanism of the lungs is effective when the plasma dopamine level becomes sufficiently high, and that the lungs clear 19%–21% of clinical doses of dopamine.

Key Words: LUNGS, METABOLIC FUNCTION—dopamine uptake. SYMPATHETIC NERVOUS SYSTEM, PHARMACOLOGY—dopamine.

The lung is an efficient "biochemical filter" for central venous blood (1). The partial removal of norepinephrine during pulmonary transit is, for example, now well-established both in animals (2-4) and in humans (5,6). Pulmonary uptake of dopamine and epinephrine is still, however, controversial. In humans, Sole et al. (5) found that approximately 25% of circulating norepinephrine was extracted during one passage through the lungs in normal resting humans, whereas neither epinephrine nor dopamine was affected. On the other hand, Russel et al. (6) measured the pulmonary clearance of catecholamines (CAs) in critically ill patients in whom the mixed venous concentrations of endogenous norepinephrine, epinephrine, and dopamine were extremely high and concluded that the pulmonary circulation had a substantial clearance mechanism for all three CAs. Although the reason for this discrepancy is not clear, it is possible that clearance may be dependent on the plasma level of CAs.

The present study was designed to analyze quantitatively the pulmonary contribution to the clearance of exogenous dopamine in humans. Both clearance

by the lungs and total plasma clearance of dopamine were determined with varying concentrations of plasma dopamine.

Methods

The subjects of this investigation were 26 ASA physical status I or II patients with esophageal cancer, aged 42–73 yr and weighing 42–68 kg, who were scheduled for radical operations. The protocol was approved by the hospital's institutional human investigation committee, and written informed consent was obtained from each patient. All of the patients were screened for parenchymal lung disease on the basis of clinical history, chest x-ray, pulmonary function test, and arterial blood gas analysis. If such were found, they were excluded from the study. Patients with pulmonary hypertension (mean pulmonary artery pressure ≥22 mm Hg) at the time of pulmonary artery catheter insertion were also excluded from the study.

Premedication consisted of 1 mg/kg hydroxyzine and 0.5 mg atropine, given intramuscularly, 1 h before scheduled time of surgery. Anesthesia was induced with 4–5 mg/kg thiopental and maintained with 67% nitrous oxide in oxygen supplemented with 0.8%–1.2% end-tidal enflurane. Tracheal intubation was facilitated with 1 mg/kg intravenous succinylcho-

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line, and abdominal muscle relaxation was maintained with 0.1 mg/kg intravenous pancuronium, as required. Ventilation was controlled to maintain endtidal CO₂ tension at 35 mm Hg (Nelcor N-1000). Pulmonary arterial and radial arterial catheters were inserted for continuous monitoring of vascular pressures and for obtaining blood samples. Intravenous fluids were administered as needed to maintain a constant central venous pressure. Rectal temperature was maintained between 35 and 37°C by using a circulating water blanket and by adjusting room temperature. Arterial blood gas analysis and measurement of serum electrolytes were carried out frequently to maintain a pH of 7.35–7.45, serum Na⁺ of 130-145 mEq/L, and serum K^+ of 3.3-4.8 mEq/L. Active intervention was not necessary for most patients to maintain these ranges except for adjusting the content of Na⁺ and K⁺ in the intravenous fluids.

For measurement of the clearance of dopamine by pulmonary circulation, dopamine was administered into the subclavicular vein, and mixed venous and arterial blood samples were taken from the pulmonary artery and the radial artery for measurement of plasma dopamine. Cardiac output was determined by the thermodilution method, and plasma flow was calculated using the hematocrit value. Dopamine was diluted in 0.9% saline to a concentration of 5 mg/mL and administered by a constant-volume infusion pump (Terumo STC-523) at a constant rate. To examine the time-course of changes in the plasma level of dopamine, dopamine was administered at $1 \mu g \cdot kg^{-1} \cdot min^{-1}$ and blood samples were collected 3, 5, 10, 15, 20, and 30 min after starting the infusion. To examine the pulmonary removal of dopamine, dopamine was infused at a rate of 0.5, 1.0, or 2.0 μ g·kg⁻¹·min⁻¹. The order of administration of each dose was randomized. The infusion was continued for about 35 min at each rate. Blood samples were collected both before starting the infusion and after 30 min of infusion at each rate. Cardiac output and hematocrit were measured before and after 30 min of infusion. An approximately 30-min resting interval was allowed between each dose.

A 3-mL blood sample was withdrawn into a precooled plastic tube containing 30 μ L of 0.2 M ethylenediaminetetraacetic acid-2Na and 0.2 M Na₂S₂O₄ and was centrifuged at 4000 rpm for 10 min at 4°C to separate the plasma. To the 1 mL of plasma, 33 μ L of 60% perchloric acid was added, and the mixture was centrifuged at 10,000 g for 30 min at 4°C. The amount of dopamine in 500 μ L of the deproteinized plasma was determined in a fully automated high-performance liquid chromatography-fluorometric system (model HLC-8030 Catecholamine Analyzer, Tosoh,

<u>Table 1</u>. Endogenous Catecholamine Levels in the <u>Plasma</u> of the Radial Artery

	Norepinephrine	Epinephrine	Dopamine
Plasma CAs (pg/mL)	420 ± 121	816 ± 200	201 ± 33

CAs, catecholamines. Values are given as mean \pm SE. n = 7 for each value.

Tokyo, Japan) using a diphenylethylene diamine condensation method (7). This assay method has a limit of sensitivity of 20 pg/mL of dopamine. The interassay and intraassay variations are less than 3%.

The calculations were based on the following relationships under steady-state conditions. Total dopamine plasma clearance = dopamine infusion dose/plasma dopamine concentration, where the plasma dopamine concentration was measured at the pulmonary artery. Pulmonary dopamine clearance = extraction fraction \times plasma flow. Extraction fraction of dopamine in passage across the lungs = $C_{\rm pa}$ – $C_{\rm ra}$ / $C_{\rm pa}$, where $C_{\rm pa}$ and $C_{\rm ra}$ are dopamine plasma concentrations in pulmonary artery and radial artery, respectively. The contribution of the lungs = pulmonary clearance/total plasma clearance.

The data are expressed as the mean \pm se. Student's *t*-test for paired data was used for statistical analysis of the transpulmonary gradient of plasma levels of dopamine. Differences among groups were analyzed by one-way analysis of variance followed by Student's *t*-test for unpaired data. A *P* value <0.05 was considered to be significant.

Results

The endogenous CA level in the plasma was measured before starting the infusion, with the results shown in Table 1. The level of endogenous dopamine was very low as compared with the level during dopamine infusion (<3%). Thus the endogenous dopamine was ignored in the determination of the pulmonary clearance of exogenous dopamine. The time-course of the change in the plasma dopamine level during the infusion of dopamine was obtained and is shown in Figure 1. At a rate of 1.0 μ g·kg⁻¹· min⁻¹, the plasma dopamine reached a nearly maximum level within 10 min and maintained an almost constant level for the next 20 min. It was considered appropriate to collect blood samples after 30 min of infusion, when the plasma level of dopamine was in a state of equilibrium.

The plasma levels of dopamine in the blood sam-

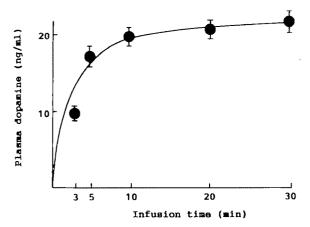


Figure 1. Time-course of change in the plasma level of dopamine during its infusion at $1 \mu g \cdot kg^{-1} \cdot min^{-1}$ (mean \pm SE, n = 5 for each point). A blood sample was obtained from the radial artery.

ples obtained simultaneously from the pulmonary artery and radial artery are shown in Table 2. The concentration of dopamine was significantly lower in the radial artery than in the pulmonary artery at the doses of 1.0 and 2.0 μ g·kg⁻¹·min⁻¹ but not at the dose of $0.5 \,\mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. There were no significant alterations in blood pressure, heart rate, cardiac output, or urine output at any of the dopamine doses. Plasma flow was calculated from the measured cardiac output and hematocrit value and showed no significant increase during the infusion as compared with the basal value. The clearance of dopamine and the contribution of the lungs are shown in Table 3. The total plasma clearance at a dopamine dose of $0.5 \ \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ was significantly greater than those at doses of 1.0 and 2.0 μ g·kg⁻¹·min⁻¹, whereas the pulmonary clearance at a dose of 0.5 μ g·kg⁻¹· min⁻¹ was smaller than those at doses of 1.0 and 2.0 μ g·kg⁻¹·min⁻¹ (not significant). The contribution of the lungs to the clearance of dopamine was 19.23% and 20.60% at doses of 1.0 and 2.0 μ g·kg⁻¹·min⁻¹, respectively, whereas there was little contribution at a dose of $0.5 \,\mu\mathrm{g}\cdot\mathrm{kg}^{-1}\cdot\mathrm{min}^{-1}$.

Discussion

The lung has a strategic position with respect to the control of a variety of vasoactive substances in blood because the lung receives the entire blood volume 1–5 times per minute in humans and it has a large vascular surface area. The control by the lungs of circulating substances is achieved by a variety of methods (8): enzymic metabolism at the endothelial surface without uptake (bradykinin, angiotensin, and adenine nucleotides), enzymic metabolism after up-

take by endothelial cells (serotonin, norepinephrine, prostaglandin E and F, and steroids), and release from the lung (prostacyclin, histamine, and kallikrein). The metabolic function of the lungs seems to have significant clinical relevance because the alveolar-capillary unit becomes a frequent focus of injury caused by environmental or vascular insults, such as hyperoxia, xenobiotic toxicity, septicemia, and adult respiratory distress in humans (1). Thus injury of the lungs possibly modifies metabolic functions (8) and influences both pathophysiological features of disease and pharmacokinetics of substrate compounds.

To estimate the removal of CAs through pulmonary circulation in humans, earlier studies (5,6) have determined the percentage of removal as the percentage of the transpulmonary difference of plasma CA to the prepulmonary plasma level. Percentage of removal calculated in this manner is considered to be useful in qualitatively assessing the ability of the organs to remove blood CAs. However, it is impossible by this method to determine the extent of the contribution of the organs to the clearance of exogenous CAs and therefore to compare quantitatively the capacity for clearance among organs. On the other hand, regional norepinephrine clearance was recently calculated in humans on the basis of fractional norepinephrine extraction by an organ and organ plasma flow using tritiated norepinephrine infusion (9). It was reported that the pulmonary fractional norepinephrine extraction was approximately 15%, and the norepinephrine clearance by the lungs accounted for about 30% of total plasma norepinephrine clearance (9).

In the present study, we determined the clearance of dopamine by the human lungs. The results show that during infusion of dopamine at 1.0 μ g·kg⁻¹·min⁻¹, the transpulmonary gradient of plasma dopamine was 12% of the prepulmonary plasma level, and the dopamine clearance by the lungs accounted for 19.2% of the total plasma dopamine clearance. The value of the contribution at a dose of 2.0 μ g kg⁻¹·min⁻¹ is similar to that at a dose of 1.0 μ g·kg⁻¹·min⁻¹, but the contribution at a dose of 0.5 μ g·kg⁻¹·min⁻¹ is far smaller than that at a dose of 1.0 μ g·kg⁻¹·min⁻¹. The results suggest that the extent of the contribution of the lungs to the clearance of circulating dopamine is dependent on the plasma level of dopamine, i.e., the clearance mechanism of the lungs works when the plasma level of dopamine becomes sufficiently high. The critical level seems to be between 9 and 25 ng/mL. It is unlikely that the assay method would be unable to detect the transpulmonary gradient of dopamine at lower plasma levels (at the dose of 0.5 μ g·kg⁻¹·min⁻¹) because the limit of sensitivity of the present assay was

Table 2. Plasma Levels of Dopamine and Pulmonary Plasma Flow During Dopamine Infusion

		Plasma levels o	f dopamine		Pulmonary
Dopamine dose $(\mu g \cdot k g^{-1} \cdot min^{-1})$	n	Pulmonary artery (ng/mL)	Radial artery (ng/mL)	Extraction plasma flow	plasma flow (mL·kg ⁻¹ ·min ⁻¹)
0.5	11	8.84 ± 0.86	8.44 ± 0.99	0.062 ± 0.045	64.96 ± 6.78
1.0	14	25.40 ± 1.23	22.34 ± 1.06^a	0.122 ± 0.027	60.52 ± 4.31
2.0	8	50.18 ± 3.60	43.71 ± 2.83^{b}	0.121 ± 0.034	58.24 ± 6.04

Extraction fraction = pulmonary artery - radial artery/pulmonary artery.

Values are given as mean ± se.

Table 3. Contribution of the Lungs to the Clearance of Dopamine

Dopamine dose (µg·kg ⁻¹ ·min ⁻¹)	n	Total plasma clearance (mL·kg ⁻¹ ·min ⁻¹)	Pulmonary clearance (mL·kg ⁻¹ ·min ⁻¹)	Contribution of the lungs (%)
0.5	11	61.93 ± 5.62	4.01 ± 3.14	4.90 ± 4.57
1.0	14	41.11 ± 2.89^a	7.05 ± 1.52	19.23 ± 3.79^a
2.0	8	41.46 ± 3.09^a	7.93 ± 2.65	20.60 ± 6.72

Contribution = pulmonary clearance/total plasma clearance.

20 pg, which is 0.25% of the plasma level at a dose of 0.5 μ g·kg⁻¹·min⁻¹.

Earlier studies based on indirect methods in dogs, such as the blood-bathed organ technique (2) and the systemic pressure response technique (3,10,11), reported that there was selective removal of norepinephrine and free passage of epinephrine and dopamine through pulmonary circulation. In contrast to these reports, recent studies based on direct measurement of the transpulmonary gradient of dopamine have demonstrated that the dog lung is able to extract dopamine from the pulmonary circulation (4,12). Sumikawa and Hirano (4) have studied dogs using the same method as was used in the present study, and demonstrated that pulmonary circulation cleared 21.5% of dopamine administered at a dose of 10 μ g·kg⁻¹·min⁻¹ and that the extent of the contribution did not change when the dose was increased to 40 μ g·kg⁻¹·min⁻¹. This value of pulmonary contribution in the dog is very similar to that found in humans in the present study. Van Shaik et al. (12) studied the pulmonary metabolism of [14C]dopamine using the bolus injection technique and concluded that 22% of [14C]dopamine was removed from the bloodstream and 14% underwent metabolic conversion within the bloodstream, resulting in a total pulmonary extraction of 36%.

The vasculature would play an important role in the clearance of infused CAs and, thus, in regulating the blood levels of circulating CAs (13,14). The removal of CAs from the circulation is considered to have some features of both neuronal (uptake 1) and extraneuronal (uptake 2) uptake. The many studies would indicate that the locally released transmitter is inactivated predominantly by uptake 1, whereas uptake 2 plays a major role in the inactivation of the circulating CAs (13). The uptake into the endothelial cells is probably the main route of dopamine removal through pulmonary circulation, as was demonstrated for norepinephrine by the radioautographic study of Nicholas et al. (15) and by the in vitro study of Rorie and Tyce (16). This mechanism would include the uptake of dopamine into the endothelial cells and intracellular metabolic conversion followed by extraction of the products into the bloodstream. Actually, the appearance of metabolites was detected through pulmonary circulation within a period of 30 s after dopamine administration in the dog (12).

It was reported that halothane and N_2O had an inhibitory effect on the norepinephrine removal in isolated perfused rabbit lungs, i.e., 1% halothane and 50% N_2O showed uptake inhibition of 23.9% and 24%, respectively (17). However, the hypothesis that halothane may inhibit neuronal or extraneuronal uptake has not been supported by other studies (18,19). In the present study the patients were anesthetized with enflurane and N_2O , but the effect of anesthetics on the dopamine clearance was not examined. It remains unclear whether the clearance mechanism for dopamine is affected by the type of anesthesia.

 $^{^{}a}P < 0.05$ versus pulmonary artery. $^{b}P < 0.01$ versus pulmonary artery.

Values are given as mean ± se.

 $^{^{}a}P < 0.05$ versus dopamine dose of 0.5 μ g·kg⁻¹·min⁻¹.

In conclusion, the lungs have a clearance mechanism for dopamine administered exogenously. This mechanism works at higher plasma concentrations of dopamine. The dopamine clearance by the lungs accounts for 19%–21% of total plasma clearance during infusion of dopamine at clinical doses.

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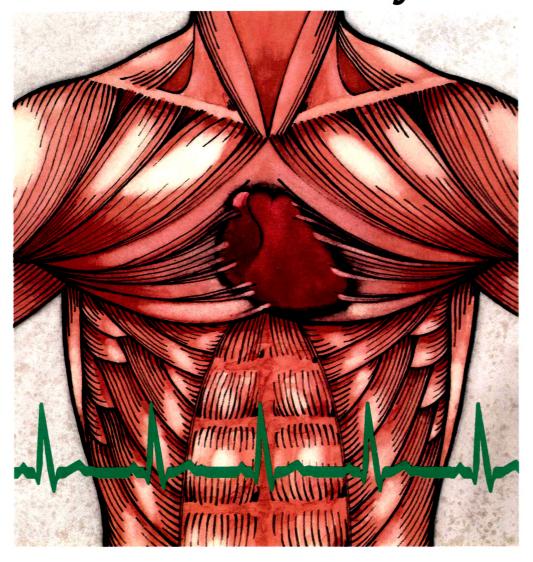
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NEW

From Burroughs Wellcome Co. A Long-Acting Neuromuscular Blocker

Excellent CV Stability



NUROMAX INJECTION (doxacurium chloride) 1 mg/mL



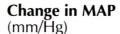
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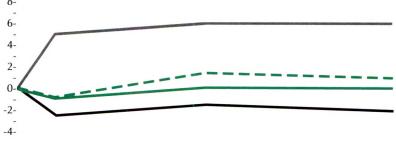
NUROMAX INJECTION

(doxacurium chloride)

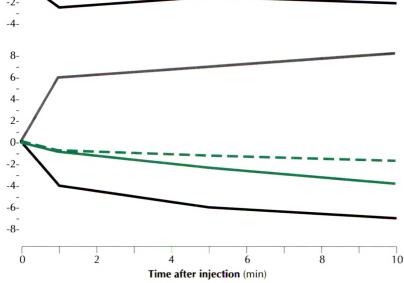
Excellent CV Stability

Cardiovascular stability comparable with vecuronium





Change in HR (beats/min)



Emmott et al¹ compared the hemodynamic effects of Nuromax 0.037 and 0.075 mg/kg with the effects of pancuronium 0.09 mg/kg and vecuronium 0.075mg/kg in 36 CABG patients (9 patients, each group).

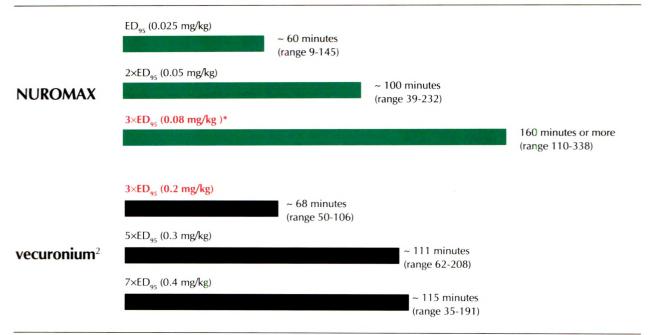
Mean changes from baseline values of mean systemic arterial pressure (MAP) and heart rate (HR) at 1, 5 and 10 min after administration. All routine cardiac and vasoactive medications were continued up to the morning of surgery.

doxacurium 0.037 mg/kgdoxacurium 0.075 mg/kgvecuronium 0.075 mg/kg



Longer acting than "high-dose" vecuronium

Clinically effective block (time to 25% recovery)



^{*}This dose should be reserved for instances in which a need for very prolonged neuromuscular block is anticipated.

- Cardiovascular stability comparable with normal saline ³
- Noncumulative
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- Vials stored at room temperature, no refrigeration required
- Supplied as a 5 mL vial, 1 mg/mL



NUROMAX ®
NJECTION
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Excellent for Long CV Procedures

NUROMAX® INJECTION (DOXACURIUM CHLORIDE)

This drug should be administered only by adequately trained individuals familiar with its actions, stics, and hazards.

DESCRIPTION: Nuromax (doxacurium chloride) is a long-acting, nondepolarizing skeletal muscle relaxant for intravenous administration. Doxacurium chloride is *trans, trans-2;* feuccinylisioxytrimethylene|bis|12,3.4 tetrahydro-6,7,8-trimethoxy-2-methyl-1-{3.4,5-trimethoxybenzyl}isoquinolinium| dichloride. The molecular formula is $C_{56}H_{78}Cl_2N_2O_{16}$ and the molecular weight is 1106.14. The compound does not partition into the 1-octanol phase of a distilled water/1-octanol system, i.e., the n-octanol-water partition coefficient is 0.

Doxacurium chloride is a mixture of three trans, trans stereoisomers, a dipair [(1R, 1'R, 2S, 2'S)] and (1S, 1'S, 2R, 2'R)] and a meso form (1R, 1'S, 2S, 2'R).

Nuromax Injection is a sterile, non-pyrogenic aqueous solution (pH 3.9 to 5.0) containing doxacurium chloride equivalent to 1 mg/mL doxacurium in Water for Injection. Hydrochloric acid may have been added to adjust pH. Nuromax Injection contains 0.9% w/v benzyl alcohol.

CLINICAL PHARMACOLOGY: Nuromax binds competitively to cholinergic receptors on the motor end-plate to antagonize the action of acetylcholine, resulting in a block of neuromuscular transmission. This action is antagonized by acetylcholinesterase inhibitors, such as neostigmine.

Pharmacodynamics: Nuromax is approximately 2.5 to 3 times more potent than pancuronium and 10 to 12 times more potent than metocurine. Nuromax in doses of 1.5 to 2 x ED₉₅ has a clinical duration of action (range and variability) similar to that of equipotent doses of pancuronium and metocurine (historic data and limited comparison). The average ED₉₅ (dose required to produce 95% suppression of the adductor politics muscle twitch response to ulnar nerve stimulation) of Nuromax is 0.025 mg/kg (range: 0.020 to 0.033) in adults receiving balanced anesthesia

The onset and clinically effective duration (time from injection to 25% recovery) of Nuromax administered alone or after succinylcholine during stable balanced anesthesia are shown in Table 1.

TABLE 1 Pharmacodynamic Dose Response* Balanced Anesthesia

		Initial Nuromax Dose (mg/kg)	•
	0.025 ¹	0.05	0.08
	(n=34)	(n=27)	(n=9)
Time to Maximum	9.3	5.2	3.5
Block (min)	(5.4-16)	(2.5-13)	(2.4-5)
Clinical Duration (min)	55	100	160
(Time to 25% Recovery)	(9-145)	(39-232)	(110-338)

Initial doses of 0.05 mg/kg ($2 \times ED_{95}$) and 0.08 mg/kg ($3 \times ED_{95}$) Nuromax administered during the induction of thiopental-narcotic anesthesia produced good-to-excellent conditions for tracheal intubation in 5 minutes (13 of 15 cases studied) and 4 minutes (8 of 9 cases studied) (which are before maximum block), respectively

As with other long-acting agents, the clinical duration of neuromuscular block associated with Nuromax shows considerable interpatient variability. An analysis of 390 cases in U.S. clinical trials utilizing a variety of premedications, varying lengths of surgery, and various anesthetic agents, indicates that approximately two-thirds of the patients had clinical durations within 30 minutes of the duration predicted by dose (based on mg/kg actual body weight). Patients ≥ 60 years old are approximately twice as likely to experience prolonged clinical duration (30 minutes longer than predicted) than patients < 60 years old; thus, care should be used in older patients when prolonged recovery is undesirable (see Geriatric Use subsection of PRECAUTIONS and Individualization of Dosages subsection of CLINICAL PHARMACOLOGY). In addition, obese patients (patients weighing ≥ 30% more than ideal body weight for height) were almost twice as likely to expenence prolonged clinical duration than non-obese patients; therefore, dosing should be based on ideal body weight (IBW) for obese patients (see Individualization of Dosages subsection of CLINICAL PHARMACOLOGY).

The mean time for spontaneous T₁ recovery from 25% to 50% of control following initial doses of Nuromax is approximately 26 minutes (range: 7 to 104, n=253) during balanced anesthesia. The mean time for spontaneous T₁ recovery from 25% to 75% is 54 minutes (range: 14 to 184, n=184).

Most patients receiving Nuromax in clinical trials required pharmacologic reversal prior to full spontaneous ery from neuromuscular block (see Antagonism of Neuromuscular Block subsection of OVERDOSAGE); therefore, relatively few data are available on the time from injection to 95% spontaneous recovery of the twitch response. As with other long-acting neuromuscular blocking agents, Nuromax may be associated with prolonged times to full spontaneous recovery. Following an initial dose of 0.025 mg/kg Nuromax, some patients may require as long as 4 hours to exhibit full spontaneous recovery.

Cumulative neuromuscular blocking effects are not associated with repeated administration of maintenance doses of Nuromax at 25% T1 recovery. As with initial doses, however, the duration of action following maintenance doses of Nuromax may vary considerably among patients.

The Nuromax ED₉₅ for children 2 to 12 years of age receiving halothane anesthesia is approximately 0.03 mg/kg. Children require higher Nuromax doses on a mg/kg basis than adults to achieve comparable levels of block. The onset time and duration of block are shorter in children than adults. During halothane anesthesia, doses of 0.03 mg/kg and 0.05 mg/kg Nuromax produce maximum block in approximately 7 and 4 minutes. respectively. The duration of clinically effective block is approximately 30 minutes after an initial dose of 0.03 mg/kg and approximately 45 minutes after 0.05 mg/kg. Nuromax has not been studied in children below the age

The neuromuscular block produced by Nuromax may be antagonized by anticholinesterase agents. As with other nondepolarizing neuromuscular blocking agents, the more profound the neuromuscular block at reversal, the longer the time and the greater the dose of anticholinesterase required for recovery of neuromuscular

nics: Administration of Nuromax doses up to and including 0.08 mg/kg (~3 x ED₉₅) over 5 to 15 seconds to healthy adult patients during stable state balanced anesthesia and to patients with serious cordiovascular riseasus patients during stature state batances a arestitesta and to patients with serious cardiovascular disease undergoing coronary after bypass graffing, cardiac valvular repair, or vascular repair produced no dose-related effects on mean arterial blood pressure (MAP) or heart rate (HR).

No dose-related changes in MAP and HR were observed following administration of up to 0.05 mg/kg Nuromax over 5 to 15 seconds in 2- to 12-year-old children receiving halothane anesthesia.

Doses of 0.03 to 0.08 mg/kg (1.2 to 3 x ED₉₅) were not associated with dose-dependent changes in mean plasma histamine concentration. Clinical experience with more than 1,000 patients indicates that adverse experiences typically associated with histamine release (e.g., bronchospasm, hypotension, tachycardia, cutaneous flushing, urticaria, etc.) are very rare following the administration of Nuromax (see ADVERSE REACTIONS)

Pharmacokinetics: Pharmacokinetic and pharmacodynamic results from a study of 24 healthy young adult patients and 8 healthy eliderly patients are summarized in Table 2. The pharmacokinetics are linear over the dosage range tested (i.e., plasma concentrations are approximately proportional to dose). The pharmacokinetics of Nuromax are similar in healthy young adult and elderly patients. Some healthy elderly patients tend to be more sensitive to the neuromuscular blocking effects of Nuromax than healthy young adult patients receiving the same dose. The time to maximum block is longer in elderly patients than in young adult patients (11.2 minutes versus 7.7 minutes at 0.025 mg/kg Nuromax). In addition, the clinically effective durations of block are more variable and tend to be longer in healthy elderly patients than in healthy young adult patients receiving the same dose.

TABLE 2 macokinetic and Pharmacodynamic Parameters' of Nuromax in Young Adult and Elderly Patients

Parameter	Healthy Young Adult Patients (22 to 49 yrs)			Healthy Elderly Patients (67 to 72 yrs)
- di ameter	0.025 mg/kg	0.05 mg/kg	0.08 mg/kg	0.025 mg/kg
	(n=8)	(n=8)	(n=8)	(n≠8)
t _{1/2} elimination	86	123	98	96
(min)	(25-171)	(61-163)	(47-163)	(50-114)
Volume of Distribution at	0.15	0.24	0.22	0.22
Steady State (L/kg)	(0.10-0.21)	(0.13-0.30)	(0.16-0.33)	(0.14-0.40)
Plasma Clearance	2.22	2.62	2.53	2.47
(mL/min/kg)	(1.02-3.95)	(1.21-5.70)	(1.88-3.38)	(1.58-3.60)
Maximum Block	97	100	100	96
(%)	(88-100)	(100-100)	(100-100)	(90·100)
Clinically Effective Duration of Block ² (min)	68	91	177	97
	(35-90)	(47-132)	(74-268)	(36-179)

Table 3 surmarizes the pharmacokinetic and pharmacodynamic results from a study of 9 healthy young adult patients, 8 patients with end-stage kidney disease undergoing kidney transplantation, and 7 patients with end-stage kidney disease; in addition, these patients may be more sensitive to the neuromuscular blocking effects of Nuromax. The time to maximum block was slightly longer and the clinically effective duration of block was represented in patients with end-stage kidney disease; in addition, these patients may be more sensitive to the neuromuscular blocking effects of Nuromax. The time to maximum block was slightly longer and the clinically effective duration of block was represented in citizents with end-stage kidney disease. of block was prolonged in patients with end-stage kidney disease.

TARIF 3 Pharmacokinetic and Pharmacodynamic Parameters' of Nuromax in Healthy Patients and in Patients Undergoing Kidney or Liver Transplantation (Isoflurane Anesthesia)

Pa	Healthy Young	Kidney	Liver
	Adult Patients	Transplant Patients	Transplant Patients
Parameter	0.015 mg/kg	0.015 mg/kg	0.015 mg/kg
	(n=9)	(n=8)	(n=7)
t _{1/2} elimination	99	221	115
(min)	(48-193)	(84-592)	(69-148)
Volume of Distribution at	0.22	0.27	0.29
Steady State (L/kg)	(0.11-0.43)	(0.17-0.55)	(0.17-0.35)
Plasma Clearance	2.66	1.23	2.30
(mL/min/kg)	(1.35-6.66)	(0.48-2.40)	(1.96-3.05)
Maximum Block	86	98	70
(%)	(59-100)	(95-100)	(0-100)
Clinically Effective Duration of Block (min)	36	80	52
	(19-80)	(29-133)	(20-91)

¹ Values shown are means (range)

No data are available from patients with liver disease not requiring transplantation. There are no significant alterations in the pharmacokinetics of Nuromax in liver transplant patients. Sensitivity to the neuromuscular blccking effects of Nuramax was highly variable in patients undergoing liver transplantation. Three of 7 patients developed ≤ 50% block, indicating that a reduced sensitivity to Nuromax may occur in such patients. In those patients who developed > 50% neuromuscular block, the time to maximum block and the clinically effective duration tended to be longer than in healthy young adult patients (see **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY).

Consecutively administered maintenance doses of 0.005 mg/kg Nuromax, each given at 25% T₁ recovery following the preceding dose, do not result in a progressive increase in the plasma concentration of doxacurium or a progressive increase in the depth or duration of block produced by each dose.

Nuromax is not metabolized in vitro in fresh human plasma. Plasma protein binding of Nuromax is approximately 30% in human plasma.

approximately 30% in numan plasma.
In vivo data from humans suggest that Nuromax is not metabolized and that the major elimination pathway is excretion of unchanged drug in urine and bite. In studies of healthy adult patients, 24% to 38% of an administered dose was recovered as parent drug in urine over 6 to 12 hours after dosing. High bite concentrations of Nuromax (relative to plasma) have been found 35 to 90 minutes after administration. The overall extent of biliary excretion is unknown. The data derived from analysis of human urine and bile are consistent with data from in vivo studies in the rat, cat, and dog, which indicate that all of an administered dose of Nuromax is recovered as parent drug in the urine and bite of these species.

Individualization of Dosages: In elderly patients or patients who have impaired renal function, the potential for In elderly patients or patients who have impaired renal function, the potential for a prolongation of block may be reduced by decreasing the initial Nuromax dose and by littrating the dose achieve the desired depth of block. In obese patients (patients weighing ≥ 30% more than ideal body weight to height), the Nuromax dose should be determined using the patient's ideal body weight (IBW), according to the following formulae:

Men: IBW in kg = [106 + (6 x inches in height above 5 feet)]/2.2

Women: IBW in kg = [100 + (5 x inches in height above 5 feet)]/2.2

Dosage requirements for patients with severe liver disease are variable; some patients may require a high than normal initial Nuromax dose to achieve clinically effective block. Once adequate block is established, the clinical duration of block may be prolonged in such patients relative to patients with normal liver function.

As with pancuronium, metocurine, and vecuronium, resistance to Nuromax, manifested by a reduced intensity and/or shortened duration of block, must be considered when Nuromax is selected for use in patients receiving phenytoin or carbamazepine (see **Drug Interactions** subsection of PRECAUTIONS).

As with other nondepolarizing neuromuscular blocking agents, a reduction in dosage of Nuromax must be considered in cachectic or debilitated patients, in patients with neuromuscular diseases, severe electrolyte abnormalities, or carcinomatosis, and in other patients in whom potentiation of neuromuscular block or difficulty reversal is anticipated. Increased doses of Nuromax may be required in burn patients (see PRE-

INDICATIONS AND USAGE: Nuromax is a long-acting neuromuscular blocking agent, indicated as an adjunct to general anesthesia, to provide skeletal muscle relaxation during surgery. Nuromax can also be used to provide skeletal muscle relaxation for endotracheal intubation.

CONTRAINDICATIONS: Nuromax is contraindicated in patients known to have hypersensitivity to it.

CONTRAINDICATIONS: Nuromax is contraindicated in patients known to have hypersensitivity to it.

WARNINGS: NUROMAX SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR
UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH THE DRUG'S
ACTIONS AND THE POSSIBLE COMPLICATIONS OF ITS USE. THE DRUG SHOULD NOT BE
ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY,
AND AN ANTAGONIST ARE WITHIN IMMEDIATE REACH. IT IS RECOMMENDED THAT CLINICIANS
ADMINISTERING LONG-ACTING NEUROMUSCULAR BLOCKING AGENTS SUCH AS NUROMAX EMPLOY
A PERIPHERAL NERVE STIMULATOR TO MONITOR DRUG RESPONSE. NEED FOR ADDITIONAL
RELAXANTS, AND ADEQUACY OF SPONTANEOUS RECOVERY OR ANTAGONISM.

Values shown are means (range). Nuromax administered after 10% to 100% recovery from an intubating dose of succinylcholine

¹ Values shown are means (range). 2 Time from injection to 25% recovery of the control twitch height.

NUROMAX HAS NO KNOWN EFFECT ON CONSCIOUSNESS, PAIN THRESHOLD, OR CEREBRATION. TO AVOID DISTRESS TO THE PATIENT, NEUROMUSCULAR BLOCK SHOULD NOT BE INDUCED BEFORE UNCONSCIOUSNESS.

Nuromax Injection is acidic (pH 3.9 to 5.0) and may not be compatible with alkaline solutions having a pH greater than 8.5 (e.g., barbiturate solutions).

Nuromax Injection contains benzyl alcohol. In newborn infants, benzyl alcohol has been associated with an increased incidence of neurological and other complications which are sometimes fatal. See Pediatric Use subsection of PRECAUTIONS.

PRECAUTIONS: General: Nuromax has no clinically significant effects on heart rate; therefore, Nuromax will not counteract the bradycardia produced by many anesthetic agents or by vagal stimulation.

Neuromuscular blocking agents may have a profound effect in patients with neuromuscular diseases (e.g., myasthenia gravis and the myasthenic syndrome). In these and other conditions in which prolonged neuromuscular block is a possibility (e.g., carcinomatosis), the use of a peripheral nerve stimulator and a small test dose of Nuromax is recommended to assess the level of neuromuscular block and to monitor dosage requirements. Shorter acting muscle relaxants than Nuromax may be more suitable for these patients.

Resistance to nondepolarizing neuromuscular blocking agents may develop in patients with burns depending upon the time elapsed since the injury and the size of the burn. Nuromax has not been studied in patients with

Acid-base and/or serum electrolyte abnormalities may potentiate or antagonize the action of neuromuscular blocking agents. The action of neuromuscular blocking agents may be enhanced by magnesium salts administered for the management of toxemia of pregnancy.

Nuromax has not been studied in patients with asthma.

No data are available to support the use of Nuromax by intramuscular injection.

Renal and Hepatic Disease: Nuromax has been studied in patients with end-stage kidney (n=8) or liver (n=7) disease undergoing transplantation procedures (see CLINICAL PHARMACOLOGY). The possibility of prolonged neuromuscular block in patients undergoing renal transplantation and the possibility of a variable onset and duration of neuromuscular block in patients undergoing liver transplantation must be considered when Nuromax is used in such patients.

when full offices is used in such palents.

Obesity: Administration of Nuromax on the basis of actual body weight is associated with a prolonged duration of action in obese patients (patients weighing ≥ 30% more than ideal body weight for height) (see CLINICAL PHARMACOLOGY). Therefore, the dose of Nuromax should be based upon ideal body weight in obese patients (see Individualization of Dosages subsection of CLINICAL PHARMACOLOGY).

Malignant Hyperthermia (MH): In a study of MH-susceptible pigs, Nuromax did not trigger MH. Nuromax has not been studied in MH-susceptible patients. Since MH can develop in the absence of established triggering agents, the clinician should be prepared to recognize and treat MH in any patient scheduled for general anesthesia

Long-Term Use in the Intensive Care Unit (ICU): No data are available on the long-term use of Nuromax in patients undergoing mechanical ventilation in the ICU.

Drug Interactions: Prior administration of succinylcholine has no clinically important effect on the neuromuscular blocking action of Nuromax.

The use of Nuromax before succinylcholine to attenuate some of the side effects of succinylcholine has not

There are no clinical data on concomitant use of Nuromax and other nondepolarizing neuromuscular blocking agents

agents. Bisoflurane, enflurane and halothane decrease the $\rm ED_{50}$ of Nuromax by 30% to 45%. These agents may also prolong the clinically effective duration of action by up to 25%.

Other drugs which may enhance the neuromuscular blocking action of nondepolarizing agents such as Nuromax include certain antibiotics (e.g., aminoglycosides, tetracyclines, bacitracin, polymyxins, lincomycin, clindamycin, colistin, and sodium colistimethate), magnesium salts, lithium, local anesthetics, procainamide, and

As with some other nondepolarizing neuromuscular blocking agents, the time of onset of neuromuscular block induced by Nuromax is lengthened and the duration of block is shortened in patients receiving phenytoin or

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis and fertility studies have not been performed. Nuromax was evaluated in a battery of four short-term mutagenicity tests. It was non-mutagenic in the Ames Salmonella assay, in the mouse lymphoma assay, and in the human lymphocyte assay. In the *in vivo* rat bone marrow cytogenetic assay, statistically significant increases in the incidence of structural abnormalities, relative to vehicle controls, were observed in male rats dosed with 0.1 mg/kg (0.625 mg/mg) Nuromax and sacrificed at 6 hours, but not at 24 or 48 hours, and in female rats dosed with 0.2 mg/kg (1.25 mg/mg) Nuromax and and sacrificed at 24 hours, but not at 6 or 48 hours. There was no increase in structural abnormalities in either male or female rats given 0.3 mg/kg (1.875 mg/m²) Nuromax and sacrificed at 6, 24, or 48 hours. Thus, the incidence of abnormalities in the *in vivo* rat bone marrow cytogenetic assay was not dose-dependent and, therefore, the likelihood that the observed abnormalities were treatment-related or clinically significant is low.

Pregnancy: Teratogenic Effects: Pregnancy Category C. Teratology testing in nonventilated, pregnant rats and mice treated subcutaneously with maximum subparalyzing doses of Nuromax revealed no maternal or fetal toxicity or teratogenic effects. There are no adequate and well-controlled studies of Nuromax in pregnant women. Because animal studies are not always predictive of human response and the doses used were subparalyzing, Nuromax should be used during pregnancy only if the potential benefit justifies the potential risk

Labor and Delivery: The use of Nuromax during labor, vaginal delivery, or cesarean section has not been studied. It is not known whether Nuromax administered to the mother has immediate or delayed effects on the fetus. The duration of action of Nuromax exceeds the usual duration of operative obstetrics (cesarean section). Therefore, Nuromax is not recommended for use in patients undergoing C-section.

Nursing Mothers: It is not known whether Nuromax is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised following Nuromax administration to a nursing

Pediatric Use: Nuromax has not been studied in children below the age of 2 years. See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION for clinical experience and recommendations for use in children 2 to 12 years of age.

Geriatric Use: Nuromax has been used in elderly patients, including patients with significant cardiovascular disease. In elderly patients the onset of maximum block is slower and the duration of neuromuscular block produced by Nuromax is more variable and, in some cases, longer than in young adult patients (see Pharmacodynamics and Individualization of Dosages subsections of CLINICAL PHARMACOLOGY).

ADVERSE REACTIONS: The most frequent adverse effect of nondepolarizing blocking agents as a class consists of an extension of the pharmacological action beyond the time needed for surgery and anesthesia. This effect may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency and apnea which require manual or mechanical ventilation until recovery is judged to be clinically adequate (see OVERDOSAGE). Inadequate reversal of neuromuscular block from Nuromax is possible, as with all nondepolarizing agents. Prolonged neuromuscular block and inadequate reversal may lead to postoperative complications

to postoperative Complications.

Observed in Clinical Trials: Adverse experiences were uncommon among the 1034 surgical patients and volunteers who received Nuromax and other drugs in U.S. clinical studies in the course of a wide variety of procedures conducted during balanced or inhalational anesthesia. The following adverse experiences were reported in patients administered Nuromax (all events judged by investigators during the clinical trials to have a possible causal relationship)

Incidence Greater than 1% - None

Incidence Less than 1% -

hypotension," flushing," ventricular fibrillation, myocardial infarction bronchospasm, wheezing

Cardiovascular Respiratory: urticaria, injection site reaction

Special Senses: diplopia

difficult neuromuscular block reversal, prolonged drug effect, fever Nonspecific:

- * Reports of ventricular fibrillation (n=1) and myocardial infarction (n=1) were limited to ASA Class 3-4 patients undergoing cardiac surgery (n=142).
- 1 0.3% incidence. All other reactions unmarked were ≤ 0.1%.

OVERDOSAGE: Overdosage with neuromuscular blocking agents may result in neuromuscular block beyond the time needed for surgery and anesthesia. The primary treatment is maintenance of a patent airway and controlled ventilation until recovery of normal neuromuscular function is assured. Once evidence of recovery from neuromuscular block is observed, further recovery may be facilitated by administration of an anticholinesterase agent (e.g., neostigmine, edrophonium) in conjunction with an appropriate anticholinergic agent (see Antagonism of Neuromuscular Block).

Antagonism of Neuromuscular Block: ANTAGONISTS (SUCH AS NEOSTIGMINE) SHOULD NOT BE ADMINISTERED PRIOR TO THE DEMONSTRATION OF SOME SPONTANEOUS RECOVERY FROM NEUROMUSCULAR BLOCK. THE USE OF A NERVE STIMULATOR TO DOCUMENT RECOVERY AND ANTAGONISM OF NEUROMUSCULAR BLOCK IS RECOMMENDED. T₄/T₁ SHOULD BE > ZERO BEFORE ANTAGONISM IS ATTEMPTED

In an analysis of patients in whom antagonism of neuromuscular block was evaluated following administration of in an analysis of patients in whom antagonism or neutoninezate block was evaluated originally assimple doses of neostigmine averaging 0.06 mg/kg (range: 0.05 to 0.075) administered at approximately 25% T_1 spontaneous recovery during balanced anesthesia, 71% of patients exhibited $T_4/T_1 \ge 0.7$ before monitoring was discontinued. For these patients, the mean time to $T_4/T_1 \ge 0.7$ was 19 minutes (range: 7 to 55). As with was discontinued. For these patients, the mean time to $1_4/1_1 \ge 0.7$ was 19 minutes (targe, 7 to 59). As with other long-acting nondepolarizing neuromuscular blocking agents, the time for recovery of neuromuscular function following administration of neostigmine is dependent upon the level of residual neuromuscular the time of attempted reversal; longer recovery times than those cited above may be anticipated when neostigmine is administered at more profound levels of block (i.e., at < 25% T_1 recovery).

Patients should be evaluated for adequate clinical evidence of antagonism, e.g., 5-second head lift, and grip strength. Ventilation must be supported until no longer required. As with other neuromuscular blocking agents, physicians should be alert to the possibility that the action of the drugs used to antagonize neuromuscular block may wear off before the effects of Nuromax on the neuromuscular junction have declined sufficiently.

Antagonism may be delayed in the presence of debilitation, carcinomatosis, and the concomitant use of certain Analysiss may be delayed in the presence of th circumstances the management is the same as that of prolonged neuromuscular block.

In clinical trials, a dose of 1 mg/kg edrophonium was not as effective as a dose of 0.06 mg/kg neostigmine in antagonizing moderate to deep levels of neuromuscular block (i.e., < 60% T₁ recovery). Therefore, the use of 1 mg/kg edrophonium is not recommended for reversal from moderate to deep levels of block. The use of pyridostigmine has not been studied.

DOSAGE AND ADMINISTRATION: NUROMAX SHOULD ONLY BE ADMINISTERED INTRAVENOUSLY.

Nuromax, like other long-acting neuromuscular blocking agents, displays variability in the duration of its effect. The potential for a prolonged clinical duration of neuromuscular block must be considered when Nuromax is selected for administration. The dosage information provided below is intended as a guide only. Doses should be individualized (see Individualization of Dosages subsection of CLINICAL PHARMACOLOGY). Factors that may warrant dosage adjustment include: advancing age, the presence of kidney or liver disease, or obesity (patients weighing ≥ 30% more than ideal body weight for height). The use of a peripheral nerve stimulator will permit the most advantageous use of Nuromax, minimize the possibility of overdosage or underdosage, and assist in the evaluation of recovery.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Adults: Initial Doses: When administered as a component of a thiopental/narcotic induction-intubation paradigm as well as for production of long-duration neuromuscular block during surgery, 0.05 mg/kg (2 x ED₉₅) Nuromax produces good-to-excellent conditions for tracheal intubation in 5 minutes in approximately 90% of patients. Lower doses of Nuromax may result in a longer time for development of satisfactory intubation conditions. Clinically effective neuromuscular block may be expected to last approximately 100 minutes on average (range: 39 to 232) following 0.05 mg/kg Nuromax administered to patients receiving balanced

An initial Nuromax dose of 0.08 mg/kg (3 x ED₉₅) should be reserved for instances in which a need for very prolonged neuromuscular block is anticipated. In approximately 90% of patients, good-to-excellent intubation conditions may be expected in 4 minutes after this dose; however, clinically effective block may be expected to persist for as long as 160 minutes or more (range: 110 to 338) (see CLINICAL PHARMACOLOGY).

f Nuromax is administered during steady-state isoflurane, enflurane, or halothane anesthesia, reduction of the Nuromax dose by one-third should be considered.

When succinylcholine is administered to facilitate tracheal intubation in patients receiving balanced anesthesia, an initial dose of 0.025 mg/kg (ED₉₅) Nuromax provides about 60 minutes (range: 9 to 145) of clinically effective neuromuscular block for surgery. For a longer duration of action, a larger initial dose may be administered.

Maintenance Doses: Maintenance dosing will generally be required about 60 minutes after an initial dose of 0.025 mg/kg Nuromax or 100 minutes after an initial dose of 0.05 mg/kg Nuromax during balanced anesthesia. Repeated maintenance doses administered at 25% T₁ recovery may be expected to be required at relatively regular intervals in each patient. The interval may vary considerably between patients. Maintenance doses of 0.005 and 0.01 mg/kg Nuromax each provide an average 30 minutes (range: 9 to 57) and 45 minutes (range: 14 to 108), respectively, of additional clinically effective neuromuscular block. For shorter or longer desired durations, smaller or larger maintenance doses may be administered.

Children: When administered during halothane anesthesia, an initial dose of 0.03 mg/kg (ED₉₅) produces maximum neuromuscular block in about 7 minutes (range: 5 to 11) and clinically effective block for an average of 30 minutes (range: 12 to 54). Under halothane anesthesia, 0.05 mg/kg produces maximum block in about 4 minutes (range: 2 to 10) and clinically effective block for 45 minutes (range: 30 to 80). Maintenance doses are generally required more frequently in children than in adults. Because of the potentiating effect of halothane seen in adults, a higher dose of Nuromax may be required in children receiving balanced anesthesia than in children receiving halothane anesthesia to achieve a comparable onset and duration of neuromuscular block. Nuromax has not been studied in children below the age of 2 years.

Compatibility: Y-site Administration: Nuromax Injection may not be compatible with alkaline solutions with a pH greater than 8.5 (e.g., barbiturate solutions).

Nuromax is compatible with:

- 5% Dextrose Injection USP 0.9% Sodium Chloride Injection USP
- 5% Dextrose and 0.9% Sodium Chloride Injection USP Lactated Ringer's Injection USP

- 5% Dextrose and Lactated Ringer's Injection
 Sufrenta" (sufrentani lotrate) Injection, diluted as directed
 Alfenta" (allentanii hydrochoride) Injection, diluted as directed
 Sublimaze" (tentanyl citrate) Injection, diluted as directed

Dilution Stability: Nuromax diluted up to 1:10 in 5% Dextrose Injection USP or 0.9% Sodium Chloride Injection USP has been shown to be physically and chemically stable when stored in polypropylene syringes at 5° to 25°C (41° to 77°F), for up to 24 hours. Since dilution diminishes the preservative effectiveness of benzyl alcohol, aseptic techniques should be used to prepare the diluted product. Immediate use of the diluted product

preferred, and any unused portion of diluted Nuromax should be discarded after 8 hours. HOW SUPPLIED: Nuromax Injection, 1 mg doxacurium in each mL.

5 mL Multiple Dose vials containing 0.9% w/v benzyl alcohol as a preservative (see WARNINGS). Tray of 10 (NDC 0081-0763-44)

STORAGE: Store Nuromax Injection at room temperature of 15° to 25°C (59° to 77°F). DO NOT FREEZE. U.S. Patent No. 4701460

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THE B.B. SANKEY ANESTHESIA ADVANCEMENT AWARD

1991 AWARDS

At the IARS 65th Congress in March 1991, the Board of Trustees announced recipients of the 1991 Award as follows:

Mitchell F. Berman, MD, Columbia University, New York, NY:

"Blockade of Cardiac Sodium Channels by Local Anesthetics. Whole-Cell and Single-Channel Analysis"

Alberto J. de Armendi, MD, AM, Massachusetts General Hospital, Boston, MA: "Mechanisms of Anaesthesia of Volatile and Barbiturate Anaesthetics at the Acetylcholine Receptor"

Stephen W. King, PhD, MD, University of California, San Francisco: "Anesthetic Effects on the Inositol Triphosphate Receptor"

Pontus Ostman, MD, The University of Iowa, Iowa City, IA:

"The Efficacy and Hemodynamic Effects of Epidurally Administered Dexmedetomidine Towards Visceral and Thermal Nociceptive Stimulus in the Gravid Guinea Pig"

Mark S. Scheller, MD, University of California, San Diego:

"Modifications of Patterns of Hippocampal Excitatory Amino Acid Concentrations Following Global Cerebral Ischemia in Rabbits by Two Voltage Dependent Calcium Channel Antagonists"

Margaret M. Sedensky, MD, Case Western Reserve University, Cleveland, OH: "Analysis of the Site(s) of Action of Volatile Anesthetics by Molecular Genetics"

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- The proposal must be within the general field of anesthesiology and may be for research, clinical care, education, or administration.
- The applicant must be a member of the International Anesthesia Research Society.
- Applications must be received in the IARS Cleveland office no later than December 13, 1991. Where relevant, applications must include institutional approval of human studies and/or animal research.
- The official application for the Award must be used. This form, as well as the guidelines for applicants, is available on request to:

International Anesthesia Research Society

2 Summit Park Dr., #140 Cleveland, OH 44131 Telephone: (216) 642-1124

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Before prescribing, please consult complete prescribing information, of which the following is

CAUTION: Federal Law Prohibits Dispensing Without Prescription.
DESCRIPTION: SUFENTA (sufentanii citrate) is a potent opioid analgesic chemically designated as N-[-4-(methoxymethyl)-1-[2-(2-thienyl)-4-piperidinyl]-N-phenylpropanamide 2-hydroxy-1,2,3-propanetricarboxylate (1:1) with a molecular weight of 578.68. SUFENTA is a sterile, preservative free, aqueous solution containing ufentanil citrate equivalent to 50 µg per ml of sufentanil base for intravenous injection. The solution has a pH range

INDICATIONS AND USAGE: SUFENTA (sufentanil citrate) is indicated: As an analgesic adjunct in the maintenance INDICATIONS AND USABLE: SUPENIA (SUPERIAN) CITED IS morcated: As an analgesic adjunct in the maintenance of balanced general anesthesia. As a primary anesthetic agent for the induction and maintenance of anesthesia with 100% oxygen in patients undergoing major surgical procedures, such as cardiovascular surgery or neurosurgical procedures in the sitting position, to provide favorable myocardial and cerebral oxygen balance or when extended postoperative ventilation is anticipated. SEE DOSAGE CHART FOR MORE COMPLETE INFORMATION ON THE USE OF SUFFINE.

CONTRAINDICATIONS: SUFENTA is contraindicated in patients with known hypersensitivity to the drug.
WARNINGS: SUFENTA should be administered only by persons specifically trained in the use of
intravenous anesthetics and management of the respiratory effects of potent opioids. An opio
antagonist, resuscitative and intubation equipment and oxygen should be readily available.

Intravenous anesthetics and management of the respiratory effects of potent opicids. An opicid antagonist, resuscitative and intubation equipment and oxygen should be readily available. SUFENTA may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is dose related. Administration of SUFENTA may produce muscular rigidity that may re rapid onset than that seem with fentanyl. SUFENTA may produce muscular rigidity that may be skeletal muscles of the neck and extremities. The incidence can be reduced by: 1) administration of up to ½ of the full paralyzing dose of a non-depolarizing neuromuscular blocking agent blocking agent blocking agent blocking agent following loss of consciousness when SUFENTA is used in anesthetic dosages (above 8 µg/kg) titrated by slow intravenous infusion, or, 3) simultaneous administration of SUFENTA and a full paralyzing dose of a neuromuscular blocking agent when SUFENTA is used in rapidly administered anesthetic dosages (above 8 µg/kg). The neuromuscular blocking agent when SUFENTA is used in rapidly administered anesthetic dosages (above 8 µg/kg). The neuromuscular blocking agent when SUFENTA is used in rapidly administered succlusifies should be available for postoperative monitoring and ventilation of patients administered SUFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

PRECAUTIONS: General: The initial dose of SUFENTA should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. Vital signs should be monitored routinely. Nitrous oxide may produce cardiovascular depression when given with high doses of SUFENTA skeletal muscle relaxant and the degree of respiratory depression and patients. The effect of the initial dose should be considered in the selection of a neuromuscular blocking agent. High doses of pancuronium may produce increases in heart rate during SUFE with head injuries. Impaired Respiration: SUFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted o controlled respiration. Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, SUFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion

Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of SUFENTA have performed to evaluate carcinogenic potential. The micronucleus test in female rats revealed that single enous doses of SUFENTA as high as 80 µg/kg (approximately 2.5 times the upper human dose) produced no

structural chromosome mutations. The Ames Salmonella typhimurium metabolic activating test also revealed no mutagenic activity. See ANIMAL TOXICOLOGY for reproduction studies in rats and rabbits.

Pregnancy Category C: SUFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects were most probably due to maternal toxicity (decreased lood consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects have been observed after administration of SUFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. SUFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of SUFENTA in labor and delivery. Therefore, such uses in the prognance of the commendation of the commendation of the data to support the use of SUFENTA in labor and delivery. Therefore, such uses in the commendation of the data to support the use of SUFENTA in labor and delivery.

is not recommended.

such use is not recommended.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SUFENTA is administered to a nursing woman.

Pediatric Use: The safety and efficacy of SUFENTA in children under two years of age undergoing cardiovascular surgery has been documented in a limited number of cases.

Animal Toxicology: The intravenous LD₅₀ of SUFENTA is 16,8 to 18.0 mg/kg in mice, 11.8 to 13.0 mg/kg in guinea pigs and 10.1 to 19.5 mg/kg in dogs. Reproduction studies performed in rats and rabbits given doses of up to 2.5 times the upper human dose for a period of 10 to over 30 days revealed high maternal mortality rates due to decreased food consumption and anoxia, which preclude any meaningful interpretation of the results.

ADVERSE REACTIONS: The most common adverse reactions of opioids are respiratory depression and skeletal muscle rigidity. See CLINICAL PHARMACOLOGY. WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity. The most frequent adverse reactions in clinical trais involving 320 patients administered SUFENTA were: hypotension (7%), hypertension (3%), chest wall rigidity (3%) and bradycardia (3%). Other adverse reactions with a reported incidence of less than 19% were:

Dermatological: Itching, erythema

Cardiovascular: tachycardia, arrhythmia astrointestinal: nausea, vomiting espiratory: apnea, postoperative respiratory Dermatological: itching, erythema Central Nervous System: chills

Miscellaneous: intraoperative muscle movement

depression, bronchospasm

DRUG ABUSE AND DEPENDENCE: SUFENTA (sufentanil citrate) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

OVERDOSAGE: Overdosage would be manifested by an extension of the pharmacological actions of SUFENTA (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. However, no experiences of overdosage with SUFENTA have been established during clinical trials. The intravengus LD₈₀ of SUFENTA in male rats is 9.34 to 12.5 mg/kg (see ANIMAL TOXICOLOGY for LD₈₀ in other species). Intravengus LD₈₀ of SUFENTA in male rats is 9.34 to 13.5 mg/kg (see ANIMAL TOXICOLOGY for LD₈₀ in other species). Intravengus administration of an opioid antagonist should not preclude more immediate countermeasures. In the event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hypo-pertilation or a nanea. A patent airway must be maintained, and a nasopharyngeal airway or endotracheal tube may

event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hypo-ventilation or apnea. A patent airway must be maintained, and a nasopharyngeal airway or endotracheal tube may be indicated. If depressed respiration is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures may be employed.

DOSABE AND ADMINISTRATION: The dosage of SUFENTA should be individualized in each case according to body weight, physical status, underlying pathological condition, use of other drugs, and type of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of SUFENTA should be determined on the basis of lean body weight. Dosage should be reduced in elderly and debilitated patients (see PRECAUTIONS). Vital signs should be monitored routinely. Protect from light. Store at room temperature 15°-30° C (59°-86° F)

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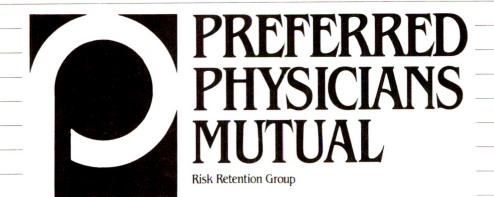
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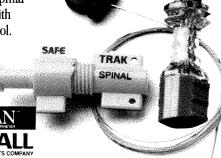
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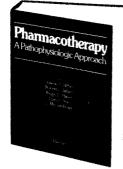
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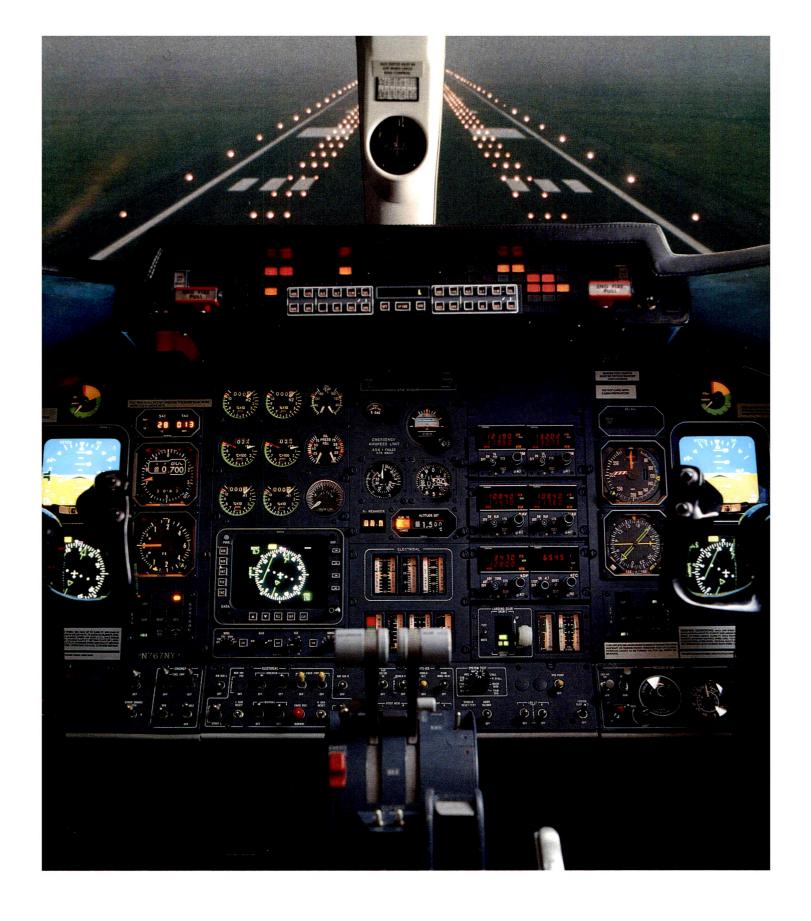
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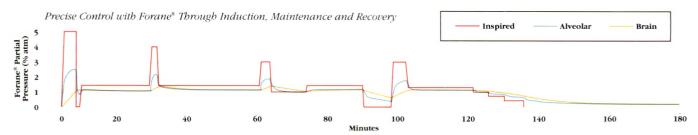
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DESCRIPTION
FORAME (isoflurane, USP) a nonflammable liquid administered by vaporizing, is a general inhalation anesthetic drug
bits 1-chloro-2-2.2 trifluoroethyl difluoromethyl ether, and its structural formula is.

Some physical constants are

Molecular weight		184 5
Boiling point at 760 mm Hg		48.5 °C (uncorr.)
Refractive index n _p ²⁰		1 2990-1 3005
Specific gravity 25 °/25 °C		1 496
Vapor pressure in mm Hg**	20 °C	238
	25 °C	295
	30 °C	367
	35 °C	450

	35 -C	430
"Equation for vapor pressure calcu	lation	
$\log_{10}P_{\text{vap}} + A + \frac{B}{T}$ where	A ~ 8056 B = -1664.58 T = °C + 273.16 (Kelvin)	
Partition coefficients at 37 °C		
Water/gas		0.61
Blood/gas		1 43
Oil/gas		908
Partition coefficients at 25 °C - rubt	per and plastic	
Conductive rubber/gas	•	620
Butyl rubber/gas		75.0
Polyvinyl chloride/gas		110.0
Polyethylene/gas		~2.0
Polyurethane/gas		~14
Polyolefin/gas		~11
Butyl acetate/gas		~25
Purity by gas chromatography		>99.9%

Lower limit of flammability in oxygen or nitrous oxide at 9 joules/sec and 23 ° Lower limit of flammability in oxygen or nitrous oxide at 900 joules/sec and 23 °

None Greater than useful concentration in anesthesia

nitrous oxide at 900 joules/sec and 23.°

concentration in anesthesia an anest a clear, coordiness stable liquid containing no additives or chemical stabilizers Isoflurane has a mildly pungent ethereal odor. Samples stored in indirect sunlight in clear, coloriess glass for five years, as well as samples directly a for 30 hours to 2 amp. 115 voil, 60 cycle long wave UV light were unchanged in composition as determined chromatography Isoflurane in one normal sodium methoside-methanol solution, a strong base, for over six months med essentially no ability. Indicative of strong base stability Isoflurane does not decompose in the presence of me, and does not attack aluminum. Int. Drass, iron or copper.

Age	100% Oxygen	70% N₂O 056	
26 + 4	1.28		
44 ± 7	1 15	0.50	
	1.00	0.00	

Induction of and recovery from isoflurane anesthesia are rapid Isoflurane has a mild pungency which limits the rate of induction, although excessive salivation or tracheobronchial secretions do not appear to be stimulated Pharyngia and laryngiae reflexes are readily obtunded. The level of anesthesia may be changed rapidly with isoflurane is a profound respiratory depressant. RESPIRATION MUST BE MONITORED CLOSELY AND SUPPORTED WHILE IN INCUSSARY As amenthetic done is increased, tidal volume decreases and respiratory rate is unchanged. This depression is partially reversed by strigical stimulation, even at deeper levels of anesthesiae Isoflurane colore a uph response reminiscent of that seen with distriby either and enflurane. Stribough the frequency is less than with enflurane information.

remunscent of that seen with diethyl ether and enflurane, although the frequency is less than with enflurane Blood pressure decreases with induction of anesthesis but returns toward normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding decreases in blood pressure. Nitrous could ediminishes the inspiration would be a second result of the second results of the progressive interests and the second results of the se

Muscle relaxation is often adequate for intra-abdominal operations at normal levels of anesthesia. Complete muscle paralysis can be attained with small doses of muscle relaxants ALL COMMONITY USED MUSCLE RELAXANTS ARE MARKEDLY POTENTIATED WITH ISOFLURANE. THE EFFECT BEING MOST PROFOUND WITH THE NONDEPOLARIZ-ING TYPE. Neostigmine reverses the effect of nondepolarizing muscle relaxants in the presence of isoflurane All commonly used muscle relaxant are compatible with isoflurance.

inonity used muscie relaxants are compatible with isoflurane isoflurane can produce coronary vasodilation at the arteriola level in selected animal models 1.2, the drug is probably also a contant vilator in humans isoflurane i.ble some other coronary arteriolar dilators, has been shown to divert blood from collateral dependent myocardium to normally perfused areas in an animal model ("coronary steal"). Climas studies to date evaluating myocardial ischemia, infarction and death as outcome parameters have not established that the coronary arteriolar dilators property of isoflurane is associated with coronary steal or myocardial ischemia in petents with coronary arteriolar diesse.

Pharmacokinstics: isoflurane undergoes minimal biotransformation in man. In the postanesthesia period, only 0.17% of the isoflurane taken up can be recovered as urinary metabolites.

INDICATIONS AND USAGE

USP) may be used for induction and maintenance of general anesthesia. Adequate data have to establish its application in obstetrical anesthesia.

CONTRAINDICATIONS

sitivity to FORANE (isoflurane, USP) or to other halogenated agents

Known or suspected genetic susceptibility to malignant hyperthermia.

WARNINGS

Since levels of anesthesia may be altered easily and rapidly, only vaporizers producing predictable concentrations should be used. Hypotension and respiratory depression increase as anesthesia is deepened.

increased blood loss comparable to that seen with halothane has been observed in patients undergoing abortions FORANE (isoflurane, USP) markedly increases cerebral blood flow at deeper levels of anesthesia. There may be a transient rise in cerebral spinal fluid pressure which is fully reversible with hyperventilation.

PRECAUTIONS

PRECAUTIONS

General: As with any potent general anesthetic, FORANE (isoflurane, USP) should only be administered in an adequately equipped anesthetizing environment by those who are familiar with the pharmacology of the drug and qualified by training and experience to manage the anesthetized patient.

by training and experience of minage the americans produced for the anesthetics employed, maintenance of normal hemodynamics is important to the avoidance of myocardial ischemia in patients with coronary artery disease^{4,5,6,7}

Information to Patients: Isoflurane, as well as other general anesthetics, may cause a slight decrease in intellectual function for 2 or 3 days following anesthesia. As with other anesthetics, small changes in moods and symptoms may persist for up to 6 days after administration.

Laboratory Tests: Transient increases in BSP retention, blood glucose and serum creatinine with decrease in BUN, serum cholesterol and alkaline phosphatase have been observed.

Drug Interactions: Isoflurane potentiates the muscle relaxant effect of all muscle relaxants, most notably nondepolarizing muscle relaxants, and MAC (minimum alveolar concentration) is reduced by concomitant administration of N₂O See CLINICAL PHARMACOLOGY

See CLINICAL PHARMACOLOGY

Carcinogenesis. Swiss ICR mice were given isoflurane to determine whether such exposure might induce neoplasia isoflurane was given at 1/2, 1/8 and 1/32 MAC for four in-utero exposures and for 2/4 exposures to the pups during the first nine weeks of life. The mice were killed at 15 months of age. The incidence of tumors in these mice was the same as in untreated control mice which were given the same background gases, but not the anesthetic.

Pregnancy Category C: Isoflurane has been shown to have a possible anesthetic-related fectorize effect in mice when given in doses 6 times the human dose. There are no adequate and well-controlled studies in pregnant women Isoflurane should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when isoflurane is administered to a nursing woman

in human milk, caution should be exercised when isoflurane is administered to a nursing woman Malignant Ryperthermia: In susceptible individuals, isoflurine anesthesia may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. The syndrome includes nonspecific features such as muscle rigidity, Leckhogards, tachypene, synaosis, arrhythmias unstable blood pressure III should also be noted that many of these nonspecific sugns may appear with light anesthesia, acute hypoxia, etc., I an increase in overall metabolism may be reflected in an elevated temperature (which may reapidly early or late in the case, but usually is not the first sign of augmented metabolism) and an increased usage of the CO₂ absorption system (hot cansiste) PaO₂ and pH may decrease, and hypertalemia and a base deficit may appear. Treatment includes discontinuance of triggering agents (e.g., isoflurane), administration of intravenous dantrolene sodium and application of supportive therapy. Such therapy includes vigorous efforts to restore body temperative to normal, respiratory and circulatory support as indicated, and management of electrolyte-fluid-acid-base derangements (Consult prescribing information for dantrolene sodium intravenous for additional information on patient management.) Renai failure may appear later, and urine flow should be sustained if possible

ADVERSE REACTIONS
Adverse reactions encountered in the administration of FORANE (isoflurane, USP) are in general dose dependent extensions of pharmacophysiologic effects and include respiratory depression, hypotension and arrhythmias

Shivering, nauses, vomiting and ileus have been observed in the postoperative period

As with all other general anesthetics, transient elevations in white blood count have been observed even in the absence of surgical stress.

See PRECAUTIONS for information regarding malignant hyperthers

OVERDOSAGE

nt of overdosage, or what may appear to be overdosage, the following action should be taken

Stop drug administration, establish a clear airway and initiate assisted or controlled ventilation with pure oxygen

DOSAGE AND ADMINISTRATION

Premedication: Premedication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by FORANE (isoflurane, USP) and the heart rate tends to be increased. The use of anticholinergic drugs is a matter of choice.

Inspired Concentration: The concentration of isoflurane being delivered from a vaporizer during anesthesia should be known. This may be accomplished by using

- vaporizers from which delivered flows can be calculated, such as vaporizers delivering a saturated vapor which is then diluted. The delivered concentration from such a vaporizer may be calculated using the formula

% isoflurane
$$\begin{array}{lll} \text{ **} & \text{ isoflurane } & \text{ **} & \frac{100 \text{ P}_{\text{V}} \text{ F}_{\text{V}}}{\text{F}_{\text{T}} \text{ (P}_{\text{A}} - \text{P}_{\text{V}})} \\ \text{where } & \text{P}_{\text{A}} \times & \text{Pressure of atmosphere } \\ & \text{P}_{\text{V}} \times & \text{Vapor pressure of isoflurane } \\ & \text{F}_{\text{V}} \times & \text{Flow of dgs through vaporizer (mL/min)} \\ & \text{F}_{\text{T}} \times & \text{Total gas flow (mL/min)} \end{array}$$

Isoflurane contains no stabilizer. Nothing in the agent alters calibration or operation of these vaporizers

Induction: Induction with isoflurane in oxygen or in combination with oxygen introus oxide mixtures may produce coughing, breath holding, or laryngospaam. These difficulties may be avoided by the use of a hypnotic dose of an ultra short-acting parbiturate. Inspired concentrations of 1.5 to 3.0% isoflurane usually produce surgical anesthesia in 7.to 10 minutes.

Maintenance: Surgical levels of an esthesia may be sustained with a 1 0 to 2 5 % concentration when nitrous oxide is us ed concomitantly. An additional 05 to 1 0 % may be required when isofluriants is given using oxygen alone. If added relaxation is required, supplemental doses of muscle relaxants may be used.

The level of blood pressure during maintenance is an inverse function of isoflurane concentration in the absence of other complicating problems. Excessive decreases may be due to depth of anesthesia and in such instances may be corrected by lightning anesthesia.

urane, USP), NDC 10019-360-40, is packaged in 100 mL amber-colored bottles.

Storage: Store at room temperature 15 $^{\circ}$ - 30 $^{\circ}$ C (59 $^{\circ}$ - 86 $^{\circ}$ F) isoflurane contains no additives and has been demonstrated to be stable at room temperature for periods in excess of five years.

•Gerences
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What Solvent Best Represents the Site of Action of Inhaled Anesthetics in Humans, Rats, and Dogs?

Shahram Taheri, BS, Michael J. Halsey, PhD, Jin Liu, MD, Edmond I. Eger II, MD, Donald D. Koblin, PhD, MD, and Michael J. Laster, DVM

TAHERI S, HALSEY MJ, LIU J, EGER EI II, KOBLIN DD, LASTER MJ. What solvent best represents the site of action of inhaled anesthetics in humans, rats, and dogs? Anesth Analg 1991;72:627–34.

The correlation between the potency of inhaled anesthetics and their solubility in a hydrophobic phase provides an opportunity to define better the characteristics of the anesthetic site of action. The correlation implies that inhaled anesthetics act in a hydrophobic site and that the solvent used has properties representative of the true site of anesthetic action. We sought to characterize this site more accurately by testing for the solvent that provided the best correlation for a diverse group of anesthetics. We determined the solubility of halothane, enflurane, cyclopropane, fluroxene, isoflurane, sevoflurane, and desflurane in benzene, olive oil, Intralipid, n-octanol, and lecithin. We used established MAC values for rats, dogs, and humans for all but sevoflurane and desflurane, for which we determined MAC in rats to be $2.80\% \pm 0.24\%$ (mean \pm standard

deviation) and 7.71% \pm 0.65%, respectively. Lecithin gave the lowest coefficient of variation for the product of potency (MAC) \times solubility, but the difference was statistically significant only for a comparison of the products for lecithin and olive oil. The values for lecithin were within the range of values produced by biological variation. More important, the correlation of log MAC and log solubility had an average slope of unity (-1.04 ± 0.07) for lecithin, but a slope differing from unity for benzene (-0.82 ± 0.05) and olive oil (-0.87 ± 0.05). We conclude that lecithin is probably more representative of the site of action of these anesthetics than the other solvents.

Key Words: ANESTHETICS,

VOLATILE—cyclopropane, desflurane, enflurane, fluroxene, halothane, isoflurane, sevoflurane. ANESTHETICS, VOLATILE—theories of narcosis. THEORIES OF ANESTHETIC ACTION, LIPID SOLUBILITIES.

The relationship between anesthetic potency and hydrophobicity was described by Meyer (1) and Overton (2) at the turn of this century. The correlation may be described by the formula: anesthetizing partial pressure (e.g., MAC for a given species) × lipid solubility = a constant. This constant varies by a factor of approximately 2 or 3, with a coefficient of variation of 31% in dogs or 24% in humans for potencies ranging over 100,000-fold (3). The reliability of this relationship between potency and hydrophobicity suggests that inhaled anesthetics act in a hydrophobic phase, one mimicked by lipids such as olive oil.

Targ et al. have suggested that this relationship

may differ or vary according to the series of compounds studied (4). Within a series of halogenated methyl-ethyl ethers tested in rats, the product of rat-MAC \times solubility in olive oil was 120 \pm 11 (mean ± standard deviation), whereas the product for other conventional agents such as enflurane, halothane, fluroxene, and cyclopropane was 238 ± 26. Their findings suggest that there may be regular deviations from the relationship of potency and lipid solubility, and a bimodal form of distribution indicates two (or more) possible sites of anesthetic action. These data raise the issue of the adequacy of the model solvent used to characterize the site of action. Targ et al., as have many previous investigators, used olive oil, which is an inconsistent mixture of various lipids (5). Several researchers have suggested that other solvents, particularly more polar solvents or membranes per se might be more representative of the anesthetic site of action (6-12).

The present study examines several different sol-

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Address correspondence to Dr. Eger, Department of Anesthesia, S-455, University of California, San Francisco, CA 94143-0464.

vents thought to approximate more closely the site of action. Our purpose was to determine whether the use of such solvents would decrease the variability in the relationship between anesthetic solubility and potency and/or eliminate the bimodal distribution noted by Targ et al. A decrease in variability for a given solvent would suggest that the solvent was more representative of the site of anesthetic action and might provide new insights into the physical characteristics of that site. In addition, were the variability to decrease to a level parallel to that of biological variability, this would imply the ability to predict relatively precisely the potency of new, untested anesthetics.

Methods

We studied the solubilities (partition coefficients) of halothane, enflurane, cyclopropane, fluroxene, isoflurane, sevoflurane, and desflurane in four liquid solvents and one solid "solvent." The solvents were olive oil, Intralipid (20%), *n*-octanol, benzene, and refined soybean lecithin (ICN Biochemicals, Cleveland, Ohio). All solubility values were determined in quadruplicate, except as noted. The solubilities in the first three solvents were determined as follows.

We first established a calibration tank for each of the above anesthetics by injecting liquid agent into E or H cylinders that were then pressurized with nitrogen or oxygen. The concentrations of the anesthetics in these tanks were assayed by comparing the peak heights obtained by gas chromatography for samples from the tanks against primary standards established by volumetric techniques. Gases from the tanks were used both for calibration and as a source of anesthetic. Four 580-mL flasks (the volume [VF] of each flask was determined by weighing each flask empty and then filled with water) were prepared by cleaning them and their Teflon stoppers with soap and water. Each stopper was pierced with two needles capped with a one-way stopcock; one needle was used for injection of solvent and the other for drawing samples from the flask. The soap was removed with several rinsings of distilled water, and the flasks, stoppers, and needles were dried. A thin line of Teflon stopcock grease was then applied as a circle at and around the upper third of the stopper. This sealed the stopper against the ground glass entrance to the bottle. At the point where the needles pierced the flask we applied a ring of Teflon stopcock grease to ensure a seal. The flask was evacuated to approximately one-third of an atmosphere and placed in a waterbath at 37°C for 30 or more minutes.

Gas-tight glass syringes with three-way stopcocks were calibrated (volume = VS) by measuring the weight to 1 (1-mL syringe), 5 (5-mL syringe), or 10 (10-mL syringe) mL with and without water. A 5-mL syringe was used for Intralipid and *n*-octanol studies. A 1-mL syringe was used for olive oil studies except that a 5-mL syringe was used in the determination of the fluroxene partition coefficient and a 10-mL syringe was used in the determination of the desflurane partition coefficient. Four 30- or 50-mL uncalibrated syringes, each fitted with a three-way stopcock, also were prepared by cleaning the barrel and plunger with hot soapy water and rinsing several times with distilled water.

To determine anesthetic solubility in olive oil for all agents but desflurane, we prepared a stock solution of olive oil with anesthetic by placing 20 mL of olive oil in a 50-mL syringe (capped with a three-way stopcock) and adding 0.05–0.3 mL of liquid anesthetic or 20 mL of 100% cyclopropane to it. Desflurane determinations required 125 mL of stock solution. Each mixture was shaken vigorously. Four to five milliliters of the stock solution was injected into each of the 30-mL uncalibrated syringes, and for desflurane 12-14 mL was injected into each of the 50-mL uncalibrated syringes. Fifteen milliliters of room air (gas) was added to these syringes and the three-way stopcocks were closed. The oil and gas were shaken vigorously, and each syringe was placed in a tonometer in a waterbath at 37°C. Every 15 min for 1-1.5 h, the syringe was removed from the tonometer, shaken vigorously for 5-10 s, and immediately replaced in the tonometer in the waterbath.

To determine anesthetic solubility in Intralipid and *n*-octanol, we placed 20 mL of the solvent in each of four 30-mL syringes. Ten milliliters of calibration gas was added to each syringe, the mixture was shaken vigorously and the gas then ejected. Another 10 mL of calibrating gas was added, the mixture shaken vigorously, and the syringe placed in the tonometer in the waterbath at 37°C. Every 15 min for 1–1.5 h, the syringe was removed from the tonometer, shaken vigorously for 5–10 s, and immediately replaced in the tonometer in the waterbath.

When this process was completed, the syringe containing the solvent and gas was removed from the tonometer and placed in the waterbath in an upright or slanted upright position such that the three-way stopcock protruded from the surface of the water. This allowed the solvent to drain from the vicinity of the stopcock. The parts of the three-way stopcock open to air were cleared of water by blowing air through it.

The gas in the syringe was analyzed for anesthetic

concentration (CS) as follows: the gas was injected into a 0.1-mL gas sampling loop of a gas chromatograph via a nylon catheter. A Gow-Mac series 580 gas chromatograph with a column composed of 10% SF-96 on Chromasorb WHP, 68/80-mesh, 0.32-cm internal diameter by 6.1 m, and maintained at 48°C was used. A nitrogen carrier stream flowing at 15 mL/min was delivered through the column to a flame ionization detector at 150°C, supplied by hydrogen at 20 mL/min and by air at 200 mL/min. Calibration (tank) standards were injected at intervals during each study. Peak heights were proportional to concentration over the entire range of the concentrations studied. Immediately after injection of the gas sample from the syringe, the remaining gas was ejected from the syringe, leaving only solvent plus dissolved anesthetic.

Next, we connected the calibrated syringe by its stopcock to the three-way stopcock on the syringe containing the equilibrated solvent. We cleared the dead space of the calibrated syringe by injecting a small volume (0.5–1.5 mL) of the solvent into the calibrated syringe, ejecting this small amount plus any air that had entered with the solvent. The calibrated syringe was filled to the mark, the three-way stopcock was closed, and the dead space of the three-way stopcock cleared. The three-way stopcock with calibrated syringe was connected to one of the evacuated 580-mL flasks and all the solvent plus dissolved anesthetic was drawn or injected into the flask. Air was allowed to enter the flask until the pressure in the flask was slightly below atmospheric.

The flask was removed from the waterbath, rapidly rotated to layer the solvent and dissolved anesthetic on the inside walls, and replaced in the waterbath. This process was repeated four times at 15-min intervals. After the third time, the one-way stopcock on the flask was opened to allow the pressure in the flask to equal ambient pressure. After the fourth layering, a fresh 30-mL syringe (plus three-way stopcock) containing 20 mL of air was attached to the one-way stopcock on the flask that had not been used to convey the solvent into the flask. Twenty milliliters of gas was added to each flask and mixed with the gases within the flask by injecting and withdrawing this volume 20 times back and forth into the 30-mL syringe. The concentration of anesthetic in the final 20 mL in the syringe (CF) was analyzed by gas chromatography.

The partition coefficient was calculated as:

$$[(VF \times 20 \text{ mL} - VS)/VS][CF/(CS - CF)],$$

where VF is the volume of the flask, VS is the volume of the calibrated syringe, CF is the anesthetic concen-

tration in the flask, and CS is the anesthetic concentration in the syringe.

Lecithin partition coefficients were determined as follows. One hundred fifty grams of 0.5-mm glass beads was placed in each of the 580-mL flasks and the flask was weighed. Approximately 5-10 g lecithin powder was added and the flask was weighed again to give the exact weight of lecithin added. The flasks then were sealed with Teflon stoppers as they had been for the study of the liquid solvents. The flasks were evacuated to one-third of an atmosphere and placed in the waterbath at 37°C. One hundred milliliters of calibration gas was delivered into each flask. The flask was shaken vigorously and then returned to the waterbath. This shaking was repeated every 15 min for 2.5 h. At 2 or 2.25 h, the pressure in the flask was allowed to equilibrate with ambient pressure. Ten milliliters of air was added to each flask and mixed with the contents of each. Then a 10-mL sample of gas was removed and analyzed by gas chromatography. For each anesthetic, the gas chromatograph was calibrated with gas drawn from four (control) flasks prepared as just described except that the lecithin was omitted.

The partition coefficient of lecithin was calculated as follows. The concentration in the lecithin was calculated as the milliliters of anesthetic added (the average of the concentrations in the control flasks × the volumes of the flasks) minus the milliliters remaining after absorption (the concentration in each experimental flask × the flask volume corrected for the volume occupied by the glass and lecithin) divided by the volume of lecithin, taking into account the specific gravities of the glass beads (2.90 g/mL, determined by us) and lecithin (1.02 g/mL) (13). This ratio was divided by the concentration remaining in the gas phase of the flask to give the partition coefficient.

Several studies done before those described above resulted in our experimental approach. First, we documented that 2.5 h was a sufficient period of equilibration by finding that results obtained at this time did not differ from results obtained with an equilibration of 3.5 h. Second, we found that equilibration did not occur in 3.5 h in the absence of glass beads. Third, results did not differ with or without addition of 0.15 mL liquid water. Fourth, we found that equilibration was incomplete at 3.5 h when we used lecithin dissolved in chloroform and deposited on the surfaces of the flask and beads.

The method for the determination of the solubility in benzene paralleled that used for lecithin. We had originally planned to use the method applied for the other liquid solvents but found that our results were less consistent than acceptable, the standard deviation associated with these measurements being as great as 16%. We believed that this problem may have resulted from the appreciable vapor pressure of benzene and the potential for saturated vapor to condense in the several transfers needed in the determination of the partition coefficients. The substituted measurement produced similar mean values for the partition coefficients with far less variability.

The measurement of the benzene partition coefficients differed from the measurement of the lecithin partition coefficient in the following ways. No glass beads were used. An aliquot of benzene (10 mL) was drawn into the 10-mL calibrated syringe that was attached by its three-way stopcock to the one-way stopcock on the empty, evacuated 580-mL flask. The 100-mL syringe containing calibration gas for the anesthetic to be studied was attached by its three-way stopcock to the stopcock of the 10-mL calibrated syringe. The stopcocks between the flask and benzene were opened, and the plunger of the calibrated syringe was drawn back and forth 10-20 times to complete the transfer of benzene into the flask. The stopcocks between the calibration gas syringe and the flask then were opened, and the calibration gas was drawn into the flask. Finally, air was allowed to enter the flask through the three-way stopcock on the 100-mL syringe. The calibration flasks were treated in the same manner as those used for the determination of the lecithin partition coefficients except that no glass beads were placed in the flasks. The precise amount of benzene remaining after its introduction into the experimental flasks was calculated as the volume injected minus the volume vaporized as calculated from the known vapor pressure of benzene at 37°C. After introduction of the anesthetic, the flasks were treated in the same way as the flasks used for the determination of the partition coefficients of the anesthetics in the other liquid solvents. The gas samples from both the experimental and the control flasks were drawn into syringes heated above 37°C to prevent condensation of benzene. The gas within these syringes was diluted with an equal volume of room air immediately after drawing, further ensuring that condensation did not occur. The agents then were analyzed as described for the other solvents, correcting for the dilution of the sample.

MAC was determined in groups of eight 300–400-g, male, specific-pathogen-free Sprague–Dawley rats. Our study was approved by the University of California, San Francisco Committee on Animal Research. We determined MAC for desflurane and sevoflurane using the standard approach (14). A preliminary period of equilibration of at least a half

hour at a value above the MAC value, and a bracketing moving both downward and upward in concentration, assured us that we had effectively eliminated the difference between the inspired and alveolar concentrations.

Means and standard deviations were obtained for solubility and MAC. Using these values or values for MAC from other sources, we calculated the product of solubility and MAC for each of the seven agents for each of the solvents. MAC values in rats for all anesthetics but sevoflurane and desflurane were 16% cyclopropane (15,16), 4.22% fluroxene (16), 1.24% halothane (17), and 1.45% isoflurane (17). Although a value of 2.5% sevoflurane has been reported for Fischer 344 rats (18), we used Sprague–Dawley rats. For dogs, we used MAC values of 1.00% halothane (19–22), 2.2% enflurane (23–26), 18% cyclopropane (27-29), 6.3% fluroxene (28,29), 1.43% isoflurane (30-32), 2.5% sevoflurane (26,33), and 7.2% desflurane (34). For humans we used MAC values of 0.76% halothane (35), 1.68% enflurane (36), 9.2% cyclopropane (37), 3.4% fluroxene (38), 1.15% isoflurane (39), 2.05% sevoflurane (40), and 6.0% desflurane (41).

For each solvent, we calculated the mean and coefficient of variation for the product of solubility and MAC. The individual products for each solvent then were divided by the mean and this normalized value was subtracted from 1. The result was converted to an absolute number for each species and the numbers for a given solvent were summed. Thus, each solvent gave seven absolute numbers. These normalized values were compared among the solvents for differences using a Wilcoxon signed rank test.

Finally, we correlated the logarithm of the solubility values against the respective logarithm of the MAC values for each species. We compared the square of the correlation coefficients for each solvent for the three species using a paired t-test. We determined whether the slopes of the correlation differed significantly from -1, again using a paired t-test. We accepted values of P < 0.05 as indicating a significant difference.

Results

Solubilities were in the order benzene < *n*-octanol < olive oil < lecithin < Intralipid (Table 1). MAC values for desflurane (7.71% \pm 0.65%) and sevoflurane (2.80% \pm 0.24%) in Sprague–Dawley rats were greater than those previously determined in Fischer 344 (sevoflurane) or Sprague–Dawley (desflurane) rats. The relationship described by the product of

Table 1. Solubility (Phase/Gas Partition Coefficient)

Anesthetic	Benzene	Olive oil	Intralipid	n-Octanol	Lecithin
Halothane	596 ± 10	224 ± 9	41.0 ± 0.8	315 ± 17	98.6 ± 1.7"
Isoflurane	243 ± 3	88.2 ± 1.3	19.2 ± 0.4	156 ± 4	56.7 ± 2.2
Enflurane	354 ± 6	103 ± 4	22.7 ± 0.4	122 ± 2	47.9 ± 1.9
Sevoflurane	194 ± 5	47.5 ± 0.8	10.1 ± 0.3	71.0 ± 3.3	27.3 ± 0.6
Fluroxene	116 ± 7^{b}	46.4 ± 1.1	11.7 ± 0.03	61.8 ± 0.8	20.0 ± 1.7
Desflurane	51.4 ± 1.0	$17.9 \pm 0.6^{\circ}$	4.33 ± 0.08	28.5 ± 0.5	13.4 ± 0.2
Cyclopropane	24.6 ± 0.4	10.8 ± 0.3	2.45 ± 0.02	13.8 ± 0.3	7.38 ± 0.28

Values are given as the mean ± standard deviation.

Table 2. Rat MAC and the Product of MAC and Solubility

Anesthetic	MAC (% atm)	Product of MAC and solvent					
		Benzene	Olive oil	Intralipid	n-Octanol	Lecithin	
Halothane	1.24	739	278	50.8	391	122	
Isoflurane	1.45	352	128	27.8	226	82.2	
Enflurane	2.2	779	227	49.9	268	105	
Sevoflurane	2.80	543	133	28.3	199	76.4	
Fluroxene	4.22	490	196	49.4	261	84.4	
Desflurane	7.71	396	138	33.4	220	103	
Cyclopropane	16	394	173	39.2	221	118	
Mean ± sp		528 ± 171	182 ± 56	39.8 ± 10.3	255 ± 65	98.7 ± 18.0	
Coefficient of variation ^a		32.4	30.8	25.9	25.5	18.2	

^{*100} times the standard deviation divided by the mean value.

<u>Table 3</u>. Dog MAC and the Product of MAC and Solubility

Anesthetic	MAC (% atm)		rent			
		Benzene	Olive oil	Intralipid	n-Octanol	Lecithin
Halothane	1.00	596	224	41.0	315	98.6
Isoflurane	1.43	347	126	27.5	223	81.1
Enflurane	2.2	779	227	49.9	268	105
Sevoflurane	2.5	485	119	25.3	178	68.3
Fluroxene	6.3	731	292	<i>7</i> 3.7	389	126
Desflurane	7.2	370	129	31.2	205	96.5
Cyclopropane	18	443	194	44.1	248	133
Mean ± sp		536 ± 171	187 ± 66	41.8 ± 16.7	261 ± 72	101 ± 23
Coefficient of variation*		32.0	35.3	39.9	27.6	22.8

[&]quot;100 times the standard deviation divided by the mean value.

MAC × solubility was consistent over a wide range of MAC values, but the degree of consistency differed for some of the solvents (Tables 2-4; Figure 1). Data for the normalized values suggested that lecithin provided more consistent results (lower coefficient of variation) when compared with the remaining solvents. A significant difference was seen for a comparison of lecithin and olive oil (P = 0.0425). Significance was approached for the comparison of lecithin with Intralipid (P = 0.063). None of the remaining comparisons approached significance (closest was the comparison of *n*-octanol and olive oil, P = 0.091). Squared correlation coefficients differed among solvents, with higher values usually found with lecithin (0.965 ± 0.012) and *n*-octanol (0.960 ± 0.020) than with benzene (0.935 \pm 0.013), olive oil (0.919 \pm 0.031), and Intralipid (0.906 \pm 0.035). The differences were significant for the comparison of lecithin and benzene (P = 0.040), and the comparisons of noctanol and benzene (P = 0.029), olive oil (P = 0.022),

 $^{{}^{}n}_{n} = 8.$ ${}^{b}_{n} = 12.$

Table 4.	Human	MAC	and	the	Product	of	MAC	and	Solubility	

Anesthetic	MAC	Product of MAC and solvent					
	(% atm)	Benzene	Olive oil	Intralipid	n-Octanol	Lecithin	
Halothane	0.76	453	170	31.2	239	74.9	
Isoflurane	1.15	2 <i>7</i> 9	101	22.1	1 <i>7</i> 9	65.2	
Enflurane	1.68	595	173	38.1	205	80.5	
Sevoflurane	2.05	398	97.4	20.7	146	56.0	
Fluroxene	3.4	394	158	39.8	210	68.0	
Desflurane	6.0	308	107	26.0	171	80.4	
Cyclopropane	9.2	226	99.4	22.5	127	67.9	
Mean ± sp		379 ± 123	129 ± 36	28.6 ± 7.9	182 ± 40	70.4 ± 8.8	
Coefficient of variation*		32.5	27.9	27.6	22.0	12.5	

^{*100} times the standard deviation divided by the mean value.

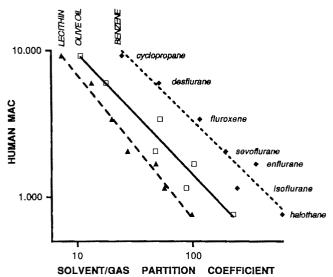


Figure 1. The logarithms of human MAC values for halotharie, isoflurane, enflurane, sevoflurane, fluroxene, desflurane, and cyclopropane (given in order of decreasing potency) correlate closely with the logarithms for their respective solubilities in olive oil, benzene, and lecithin. The highest correlation (largest r^2) is found with lecithin ($r^2 = 0.979$), and lower correlation is found with olive oil (0.946) and benzene (0.944). More important, the slope of the relationship for lecithin is -0.987 (i.e., it approaches 1.0), whereas the slopes for olive oil (-0.834) and benzene (-0.780) are distinctly less than 1.0.

or Intralipid (P = 0.027). More important, the correlation of log MAC and log solubility had an average slope of unity (-1.04 ± 0.07) for lecithin, but a slope differing from unity for benzene (-0.82 ± 0.05 ; P = 0.027) and olive oil (-0.87 ± 0.05 ; P = 0.04).

Discussion

Of the model solvents, benzene, olive oil, and Intralipid were inferior to lecithin. Despite its desirable

solubility parameter (6), benzene was no better than olive oil in predicting potency. Intralipid also did not differ significantly from olive oil despite having an aqueous component. Our finding of an excellent correlation with lecithin is consistent with the limited data reported by Lowe (11,12).

For the anesthetics studied, lecithin appeared to provide the best representation of the anesthetic site of action. Although not always statistically significant, the coefficient of variation for the product of MAC × solubility was least with lecithin, and the correlation coefficient for the relationship of log MAC and log solubility was closest to 1 for lecithin. More important, the slope for the latter relationship was not different from 1 for lecithin but differed from 1 for benzene and olive oil. A value of 1 would imply a consistent relationship to or with a site of action.

Presuming the accuracy of the determinations of anesthetic requirement (MAC) cited in Methods or determined in this study, it appears that no single solvent can precisely mimic the site of action of anesthesia in all species. This follows from an examination of the ratio of MAC for rats divided by MAC for humans, or an examination of either of the other two possible ratios (Table 5). The ratios are not consistent, having a coefficient of variation ranging from 14.1% to 22.2%. This variation is only slightly greater than the coefficient of variation for the determination of MAC (a variation of about 10%). If there is a single site of anesthetic action in a given species, its physical properties must vary from species to species, suggesting that we can only hope to find a model solvent for the site of action within a given species. This, of course, also presumes that there is a single site or multiple sites having a common physical characteristic important to the anesthetic effect.

As noted above, lecithin produced the lowest coefficient of variation of the product of MAC \times

Table 5. Ratios of MAC Values^a

		Ratios	
Anesthetic	Rat/dog	Rat/human	Dog/human
Halothane	1.24	1.63	1.32
Isoflurane	1.01	1.26	1.24
Enflurane	1.00	1.31	1.31
Sevoflurane	1.12	1.28	1.20
Fluroxene	0.70	1.24	1.85
Desflurane	1.07	1.28	1.20
Cyclopropane	0.89	1.74	1.96
Mean ± sp	1.00 ± 0.17	1.40 ± 0.20	1.44 ± 0.32
Coefficient of variation ^b	17.2	14.1	22.2

Data for these ratios are taken from Tables 3 and 4.

solubility, this value ranging from 12.5% to 22.8%. The variation in this product for lecithin appeared to approach the limit imposed by biological variation (note the similarity of the coefficient of variation for the ratios for MAC values quoted in the preceding paragraph) and our capacity to measure accurately both potency and solubility. Thus, although there may be solvents that better represent the anesthetic site of action, it may be difficult to prove that they are better than lecithin.

Why should lecithin produce the lowest coefficient of variation? In biological terms, it is one of the known constituents of central nervous system membranes. In physicochemical terms, it has both a polar and nonpolar region, again a property of all neuronal membranes. However, lecithin may not be the most representative site of anesthetic action; as suggested by Lowe (11,12), other components or combinations of components of neural membranes may be more representative.

Our results do not appear to support the hypothesis that there are two sites of anesthetic action in a particular species. Although we found a suggestion of a bimodal distribution for the product of olive oil and MAC for the human data, this bimodality did not extend to other solvents or species. Therefore, we believe that occasional bimodal distributions reflect the inadequacy of the model solvent rather than the presence of two sites of anesthetic action.

Our values for the determination of solubility in various solvents are consistent with data available from other investigators. For example, our data for olive oil are close to those reported previously (29,31,42,43). Our values for lecithin of 8.2, 20, and 94 for cyclopropane, fluroxene, and halothane, respectively, confirm those of Lowe and Hagler (11).

We redetermined the MAC values for sevoflurane and desflurane in rats for separate reasons. As indi-

cated earlier, we preferred to have the data for rats from the same strain of rats, and no previous reports had studied the potency of sevoflurane in Sprague-Dawley rats. Our value of 2.8%, however, does not differ appreciably from the 2.5% reported for Fischer 344 rats (18). We redetermined MAC for desflurane because the reported value of 5.72% (14) is less than the 6.0% value reported for humans (41). Because for all other anesthetics the MAC for humans is less than the MAC for rats (compare the data in Tables 2 and 4), we did not trust the reported 5.72% value. We have no explanation for the discrepancy between the previous and current MAC value, except that the earlier study was performed with a limited amount of agent. Attempts to conserve the agent by tightly pulling the tail of the rat through the opening from the chamber (and thereby decreasing leakage from the chamber) may have resulted in ischemia of the tail and a consequent reduction in sensitivity. We were not constrained in the present study by the supply of desflurane.

Our data suggest that a reasonable prediction of anesthetic potency may be made for a new, untested agent. However, this prediction clearly is limited in its accuracy. For the series tested, fortunately, the lowest coefficient of variation was that for humans. If these data apply more broadly, across other anesthetics, then a determination of the solubility of a new agent in lecithin should allow a prediction of potency in humans that might err by 10%–20%.

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^{*100} times the standard deviation divided by the mean value.

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Prolongation of the Pharmacologic Effect of Intrathecal Meperidine by the Use of a Lipid Solution of It

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LANGERMAN L, GOLOMB E, BENITA S. Prolongation of the pharmacologic effect of intrathecal meperidine by the use of a lipid solution of it. Anesth Analg 1991;72:635-8.

The possibility of prolonging the effect of intrathecally injected meperidine by the use of a lipid solution was examined in this study. An aqueous solution of 5% meperidine HCl, 250 µg/kg, and an equimolar solution of meperidine dissolved in iophendylate (Pantopaque) were injected subarachnoidally in two groups of rabbits (n = 9 in each) with chronically implanted catheters in the subarachnoid space at the level of L7-8. The effect of each injection was assessed by evaluation of the pain threshold in the animal's hind limbs and of the degree of motor blockade produced. The duration of analysis and of motor blockade were significantly longer when the lipid solution was used. Six of nine animals that received the aqueous solution of 5% meperidine HCl exhibited temporary signs of agitation (i.e., biting of hind limbs). None of the animals given the lipid solution of the drug did. The findings are attributed to the slow release of meperidine from the lipid phase that serves as a drug depot in the cerebrospinal fluid. The approach presented is suggested as a basis for the development of lipid solutions that might prolong the duration of spinal analgesia produced by a single intrathecal injection.

Key Words: ANESTHETIC TECHNIQUES, SPINAL—meperidine. ANALGESICS, MEPERIDINE intrathecal.

The introduction of epidural and spinal administration of morphine into clinical practice (1,2) promoted extensive research concerning the effect of opioids on the spinal cord. Spinal administration of hydrophilic narcotics such as morphine produces effective anesthesia of relatively long duration, but may result in unpredictable respiratory depression (3,4), a complication attributed to rostral spread of the agent in the cerebrospinal fluid (CSF) with direct effect on supraspinal respiratory centers. The use of watersoluble salts of lipophilic drugs is freer from the danger of respiratory depression, but the pharmacologic effect produced is relatively short, and they are not useful for producing long durations of analgesia by single injections.

In the present study, a novel approach for prolongation of the effect of intrathecal narcotics is proposed. This approach is based on the incorporation of the drug in a lipid hyperbaric solvent that acts in the CSF as a drug depot, thus prolonging the effect of the drug and possibly preventing unwarranted effects due to spread of the agent cephalad. The solvent used in this study was iophendylate (Pantopaque). This substance has had widespread use when administered intrathecally for myelography in humans and is recognized as relatively safe in this route of administration (5). In a previous study, we showed that this approach prolongs spinal anesthesia produced by tetracaine in rabbits (6). The present study was designed to determine the feasibility of the use of lipid solvents for prolongation of the effect of intrathecally injected meperidine.

Methods

Experiments were approved by the local Committee of Laboratory Animal Care and were performed in accordance with the rules and guidelines concerning the care and use of laboratory animals.

Animals

Twenty-seven adult male rabbits of mixed strain weighing 3.2-3.5 kg were used for this study. Ani-

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mals were housed individually in standard cages, had free access to food and tap water, and were kept on a 12-h light-dark cycle at a room temperature of 18°C.

Catheterization Procedure

The procedure for chronic catheterization of the subarachnoid space in the rabbit has been described in detail elsewhere (7). In brief, a 300-mm-long polyethylene catheter (PE-10, Portex) with outside diameter of 0.68 mm and inside diameter of 0.25 mm was chronically implanted in the subdural space of anesthetized rabbits, using a surgical translumbar approach, at the level of the L7-8 interspace and was directed in a caudad direction. The external end of the catheter was passed through a subcutaneous tunnel along the back of the animal and was exteriorized through an additional incision at the posterior surface of the neck. The tip of the catheter was closed with a stainless steel plug.

Experimental Protocol

The animals were examined 7–10 days after the insertion of the subarachnoid catheter. As none of the rabbits had postoperative signs of discomfort, irritability, neurologic deficits, or surgical wound infection, all were used in the study. Intrathecal injections were administered with the animals in restraining hammocks in the prone position and with the anterior portion of the body slightly elevated. Hamilton 250- μ L syringes were used with 30-gauge needles for the injections. A fixed volume of 50 μ L/kg was used for all the injections. The catheter dead space (20 μ L) was flushed with 40 μ L of normal saline solution after each injection.

The operated animals were divided into three groups of nine rabbits each. Group 1 served as controls with animals given intrathecal injections of $50~\mu\text{L/kg}$ normal saline solution. The time-course of pain threshold was evaluated after the injection. Animals in groups 2 and 3 received 2.5 mg/kg of 5% meperidine HCl (Teva, Israel) and an equimolar amount of meperidine free base dissolved in iophendylate, respectively. Pain threshold and the degree of motor blockade were evaluated at 10-min intervals after the injections. Experiments lasted 130 min. After 130 min, signs of agitation accompanied by spontaneous alterations in pain threshold were noted in some of the animals in all groups, probably due to inability of the animals to evacuate a

distended urinary bladder in the restraining hammocks.

Evaluation of Pain Threshold

Pain threshold was evaluated by application of electrical stimulus at the lateral femoral region of the animal, which had been shaved and smeared with electroconductive gel. The same site was used for all stimulations. The electrical stimulus was applied through rubber surface electrodes connected by a 100- Ω resistor to a transcutaneous electrical nerve stimulator. The intensity of the stimulus was monitored on an oscilloscope (Tektronix 564). The intensity of the applied stimuli was gradually increased until a stimulus elicited signs of withdrawal or escape response from the animal. The electrical current intensity at which such a response was detected was identified as the pain threshold of the animal. Stimuli of intensity higher than 30 mA were not applied to avoid tissue damage. In a pilot study that had been performed on six animals, the pain threshold was never below 5 mA. The minimal stimulus used in the present study was 1 mA.

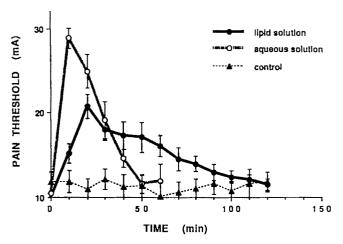
Evaluation of Motor Blockade

For the assessment of motor function, the animals were taken out of the restraining hammocks and put on the floor at 10-min intervals, and an attempt was made to walk them. Motor function was evaluated by observation of locomotion disturbances in the walking animals using criteria similar to those suggested by Feldman and Covino for dogs (8). Motor blockade was graded using a modification of the scale proposed by Bromage (9,10).

- 0 = Free movements of the animal using hind limbs without limitation or loss of balance.
- I = Limited or asymmetrical movements of the hind limbs to support the body and walk.
- II = Inability to support the back of the hind limbs despite existing ability to move the limbs and to respond to pain stimulus.
- III = Total paralysis of the hind limbs.

Statistical Analysis

Comparison of the magnitude of the pain threshold's maximum values among the groups was performed by analysis of variance, followed by Student's *t*-test.



<u>Figure 1</u>. Time-course of pain threshold after intrathecal administration of aqueous solution of meperidine (2.5 mg/kg) or of a lipid solution of meperidine free base dissolved in iophendylate. Data are mean ± sem.

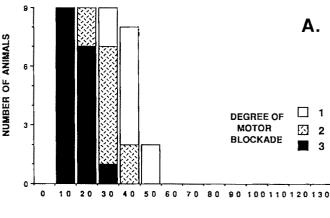
Differences in duration of pain threshold elevation relative to control between groups 2 and 3 and between duration of motor blockade were assessed by Student's t-test. Comparison between the frequencies of second and third degrees of motor blockade in groups 2 and 3 was assessed by χ^2 test. P < 0.05 was considered as the appropriate limit for statistical significance. Data are expressed as mean \pm SEM.

Results

The animals given intrathecal injections of saline solution (group 1) did not exhibit any motor dysfunction. The pain threshold ranged between 4 and 8 mA over a period of 130 min.

A significant elevation of the pain threshold (from 21.0 ± 1.9 to 57.8 ± 2.0 mA, P < 0.001) was seen in animals in which the aqueous solution of meperidine was intrathecally administered (group 2) within 10 min of the injection. This effect gradually declined, and pain threshold reached its baseline levels within 50 min of the injection. Intrathecal injection of the lipid solution of meperidine (group 3) also produced a significant elevation of pain threshold (from 19.8 ± 1.1 to 41.6 ± 2.9 mA, P < 0.001). However, in this group the maximal pain threshold was recorded 20 min after the injection and was significantly lower than the pain threshold recorded in group 2 (P < 0.005). The time-course of the changes in pain threshold in groups 2 and 3 is presented in Figure 1.

Significant differences in the duration (P < 0.001) and extent (P < 0.05) of motor blockade between groups 2 and 3 were also seen. The motor blockade



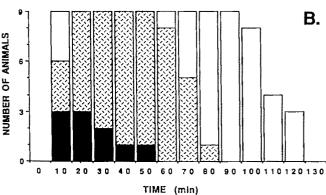


Figure 2. Time-course of the motor blockade produced by intrathecal administration of meperidine (2.5 mg/kg) in aqueous solution (A) or a lipid solution of meperidine free base dissolved in iophendylate (B). Motor blockade was evaluated according to a scale described by Bromage (9). Bars represent the number of animals (out of nine) that had motor blockade of first, second, or third degree.

produced by an injection of the aqueous solution of meperidine reached third degree in all the animals studied within 10 min of injection. The effect gradually declined and completely disappeared within 50–60 min of injection. Administration of the lipid solution of meperidine produced blockade of the third degree in three of nine animals, whereas second degree motor blockade developed in six animals. Maximal blockade occurred 10–20 min after injection. Evidence of motor blockade ceased 100–130 min after injection. The time-course of the motor blockade produced by the two solutions is presented in Figure 2.

Discussion

Analgesia owing to the direct action of opioids on receptors at the spinal cord is now a well-recognized phenomenon both clinically and in laboratory animals. Motor effects of opioids other than meperidine have been reported in animals (11,12) but not in humans. Meperidine is the only narcotic that produces significant motor blockade in both humans and animals (13,14). Meperidine is also the only narcotic that can be useful as the sole intrathecally administered agent for operative anesthesia (15,16). Both the effects of analgesia and of motor blockade served in this study for the evaluation of the pharmacologic activity of intrathecally injected meperidine.

Intrathecal administration of meperidine in an aqueous solution elicited an intense pharmacologic effect with rapid onset and relatively short duration. The spinal administration of meperidine free base in a lipid solvent produced a longer effect with moderately lower maximal intensity. The prolongation of the effect obtained by the use of a lipid solution is attributed to the sustained release of the drug from the lipid vehicle, which accumulates caudally in the spinal cord. When injected intrathecally in clinical spinal anesthesia, meperidine is administered as an aqueous solution. Therefore, the free diffusion of the drug from the injected solution in the CSF provides for rapid uptake of the drug into neural tissue, which is reflected by a rapid onset of effect. In contrast, injection of the nonionized form of meperidine in a lipid solvent of high density forms a drug depot in the CSF. The rate of diffusion of the drug into the aqueous phase of the CSF depends on the rate of its ionization, its partition coefficient, pKa, the pH of the CSF, and possibly other properties. As a result, small amounts of the hydrophobic drug are available to the neural tissue at any given time, and the rate of drug-receptor interaction is extended. Hence, the lipid solution exerts a longer effect with lower maximal activity than the aqueous solution.

In five of nine animals intrathecally given the hydrophilic solution of meperidine, signs of temporary excitation and discomfort reflected by biting of hind limbs were recorded. We believe that these changes are related to what would be itching in humans, a common side effect of intrathecally administered meperidine in humans (14–16). The absence of such effect in the animals treated with the lipid solution could be an additional reflection of lower levels of the drug in the CSF. This implies that other dose-related side effects of spinally administered drugs might be prevented by the use of their lipid solutions. We can also speculate that the side effects attributed to the spread of the drug cephalad, such as the respiratory depression and sympathetic blockade

(16), may be avoided by the use of a hyperbaric lipid solvent.

In light of these results, we believe that the development of drug formulations based on lipid vehicles is worth further evaluation. Obviously, appropriate toxicologic, pharmaceutical, and pharmacologic studies are still required before such formulations could be used in humans. We hope that the approach presented will serve as a basis for the development of a drug formulation that might produce long and safe analgesia using a single intrathecal injection.

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Deliberate Hypotension in Patients With Intracranial Arteriovenous Malformations: Esmolol Compared With Isoflurane and Sodium Nitroprusside

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ORNSTEIN E, YOUNG WL, OSTAPKOVICH N, MATTEO RS, DIAZ J. Deliberate hypotension in patients with intracranial arteriovenous malformations: esmolol compared with isoflurane and sodium nitroprusside. Anesth Analg 1991;72:639–44.

Thirty patients undergoing resection of arteriovenous malformations with deliberate hypotension were randomized to receive 1 of 3 hypotensive agents. Anesthesia was maintained with isoflurane and nitrous oxide in all patients. Mean arterial pressure was reduced 20% to 60–65 mm Hg with use of either isoflurane (\leq 4%), sodium nitroprusside (\leq 8 µg·kg⁻¹·min⁻¹), or esmolol (\leq 24 mg/min). Esmolol was associated with a decrease in cardiac output from 6.2 \pm 1.3 to 3.8 \pm 0.8 L/min, which, because of a 22% increase in systemic vascular resistance, far exceeded the reduction in mean arterial pressure. Systemic vascular resistance increased despite a 32% decrease in plasma renin activity. In contrast, with sodium nitroprusside or isoflurane, the decrease in mean arterial pressure was associated with

decreases in systemic vascular resistance of similar magnitude, with no change in cardiac output. Plasma renin activity levels increased 48% with sodium nitroprusside and 126% with isoflurane. Heart rate increased 13% with sodium nitroprusside, remained unchanged with isoflurane, and decreased 23% with esmolol. Although esmolol may be used as a primary hypotensive agent, the potential for marked myocardial depression must be recognized. The differences in pharmacologic properties for the different hypotensive agents suggest that combinations of these agents may provide a pharmacologic profile superior to either agent alone.

Key Words: ANESTHETIC TECHNIQUES, HYPOTENSIVE. ANESTHESIA, NEUROSURGICAL. ANESTHETICS, VOLATILE—isoflurane. SYMPATHETIC NERVOUS SYSTEM, PHARMACOLOGY—esmolol. PHARMACOLOGY, NITROPRUSSIDE.

Esmolol is an ultrashort acting cardioselective β -adrenergic blocker with an elimination half-life of approximately 9 min. In a previous controlled study of 25 patients undergoing spinal fusion or cerebrovascular operation, esmolol was shown to be as effective as sodium nitroprusside as the primary agent for the provision of deliberate hypotension (1). Both agents reliably reduce mean arterial pressure (MAP) to 15% below control levels obtained during maintenance anesthesia with 0.75% isoflurane. Esmolol-induced

hypotension was smooth in onset and offset, without the associated increase in heart rate seen with use of nitroprusside. In fact, patients given esmolol had an approximately 12% reduction in heart rate. Also, rebound hypertension was not seen in patients given esmolol.

In light of this previous study, esmolol might be considered an ideal hypotensive agent for patients at risk for ischemic heart disease. However, with pulmonary artery catheters not being routinely used in patients undergoing spinal fusion, the lack of invasive cardiovascular monitoring in the aforementioned study precluded this recommendation. Because esmolol is a β -blocker, the main cause of hypotension is probably a reduction in cardiac output. However, β -blockers might, through their effect on the reninangiotensin axis (2), also lead to a reduction in systemic vascular resistance, thus attenuating the

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reduction in cardiac output required for the provision of a given level of hypotension.

The present study addresses this issue by investigating the mechanism of hypotension provided by esmolol, nitroprusside, and high-dose isoflurane. Central hemodynamic data were collected by pulmonary artery catheterization, and plasma renin activity was measured in serial blood samples from patients undergoing deliberate hypotension during craniotomy for resection of intracranial arteriovenous malformations (AVM).

Methods

This study was approved by the Institutional Review Board of the College of Physicians and Surgeons of Columbia University and written informed consent was obtained from all patients. A total of 30 ASA physical status II patients with intracranial AVM scheduled for elective craniotomy were studied. Patients with a history of bronchospastic disorders, cardiac failure, significant hepatic or renal disease, atrioventricular block greater than first degree, or any other contraindication to the use of β -blockers were excluded from the study. All women of childbearing potential had negative pregnancy tests before admission into the study.

All patients were orally premedicated with 10 mg of diazepam approximately 90 min before arrival at the operating room. Once an intravenous infusion was begun, 2–5 mg of midazolam was administered approximately 15 min before induction. Electrocardiographic leads were applied, and a radial artery was cannulated before induction of anesthesia with 5–8 mg/kg of thiopental. Anesthesia was maintained with 0.75% isoflurane, end-tidal, in N₂O/O₂, 60%: 40%, with vecuronium in 10-mg increments administered as required. During initial craniotomy, isoflurane concentration was occasionally increased to a maximum of 1.2%.

After tracheal intubation, a pulmonary artery catheter was threaded through either the basilic or cephalic vein in the antecubital fossa. Cannulation was successful in 26 patients. Because of neurosurgical concerns about venous drainage of the AVM, no attempt was made to cannulate the jugular venous system.

When requested by the surgeon, deliberate hypotension was provided, but always after at least 60 min of stable maintenance anesthesia (0.75% isoflurane, end-tidal). The hypotensive level sought in this study was a 15%–25% reduction in MAP below control levels obtained just before the administration of the

hypotensive agent. Patients were randomized into three groups, based on the hypotensive agent to be used. Patients in group 1 received isoflurane in an inspired concentration from 1.5% to a maximum of 4%, those in group 2 received nitroprusside in an infusion ranging from 0.5 μ g·kg⁻¹·min⁻¹ to a maximum of 8 μ g·kg⁻¹·min⁻¹, and those in group 3 received esmolol as a 60-mg bolus over 90 s followed by an infusion of 8 mg/min. If this dose of esmolol did not lower blood pressure to the desired level after 4 min, the 60-mg bolus was repeated and followed by 16- or 24-mg/min infusions.

Measurements included mean, systolic, and diastolic blood pressures, heart rate, central venous and pulmonary capillary wedge pressures, and cardiac output by thermodilution. Systemic vascular resistance was calculated as

$$\frac{80\times (MAP-CVP)}{CO},$$

where CVP is the central venous pressure and CO is the cardiac output. In addition, arterial blood samples were obtained in prechilled test tubes containing ethylenediaminetetraacetic acid (final concentration, 3 mg/mL). Plasma was separated immediately in a refrigerated centrifuge and was frozen for later plasma renin activity analysis by radioimmunoassay (RIANEN, Du Pont Co.).

Using the paired Student's t-test, hemodynamic variables were compared within groups between the baseline just before the initiation of hypotension and the point at which a 15%–25% reduction in MAP was obtained. Comparisons between groups for demographic data and for changes induced by the various hypotensive agents were made with analysis of variance and post hoc application of Fisher's protected least significant differences. The threshold for statistical significance was taken as P < 0.05. Data are expressed as mean \pm sp.

Results

There were no significant differences between groups in age, weight, and in preinduction heart rate or blood pressure (Table 1). One patient from group 1 was resistant to isoflurane, with no significant reduction in MAP noted despite the administration of 4% isoflurane for 10 min. This patient was given propranolol (2 mg IV) and was dropped from subsequent analysis.

Hemodynamic variables and plasma renin activity before and during hypotension are compared for

Table 1. Demographic and Baseline Hemodynamic Data

	Isoflurane	Nitroprusside	Esmolol
Age (yr)	35 ± 11	35 ± 11	36 ± 8
Weight (kg)	66 ± 11	69 ± 10	70 ± 14
Heart rate (beats/min)	80 ± 17	77 ± 15	76 ± 18
Mean arterial pressure (mm Hg)	90 ± 11	92 ± 8	97 ± 10
Systolic blood pressure (mm Hg)	128 ± 16	129 ± 13	132 ± 12

Values are mean \pm so (n = 10 in each group).

each hypotensive regimen in Table 2. Comparisons between hypotensive agents are shown in Figure 1.

At baseline, just before the initiation of hypotension, all groups had similar central and peripheral blood pressures, cardiac outputs, systemic vascular resistances, and plasma renin activities. A 20% decrement to a MAP of 60–65 mm Hg was easily obtainable with all three hypotensive agents. The mean doses required were 2.3% \pm 0.7% isoflurane, endtidal; 2.3 \pm 1.3 μ g·kg⁻¹·min⁻¹ nitroprusside; and 16.8 \pm 6.2 mg/min esmolol. The changes in MAP were associated with changes in systolic and diastolic pressures that were similar in the three groups.

Esmolol hypotension was accompanied by a 23% decrease in heart rate from 88 ± 17 to 67 ± 10 beats/min (P < 0.002). Nitroprusside, on the other hand, was associated with a 13% increase in heart rate from 91 ± 23 to 103 ± 24 beats/min (P < 0.001). A 9% increase in heart rate in the isoflurane group did not achieve statistical significance (P = 0.08). Heart rates exceeding 120 beats/min were seen during deliberate hypotension in three patients given nitroprusside, in two patients given isoflurane, and in none of the patients given esmolol. Patients with persistent tachycardia were given propranolol in 1-mg increments after obtaining the hemodynamic data. The maximum heart rate seen in the esmolol group was 82 beats/min.

As to mechanism of the hypotensive effect, both nitroprusside and isoflurane caused significant decreases in systemic vascular resistance of 28% and 22%, respectively, with small changes in cardiac output that were not statistically significant. These changes in systemic vascular resistance accounted completely for the hypotensive action. In contrast, the effect of esmolol was to significantly depress cardiac output by 37% from 6.2 \pm 1.3 to 3.8 \pm 0.8 L/min (P < 0.001). There was an associated 22% increase in systemic vascular resistance with esmolol use despite a reduction in plasma renin activity from 10.4 ± 9.0 to 7.1 ± 7.4 ng·mL⁻¹·h⁻¹ (P < 0.05).

Esmolol-induced hypotension resulted in an ap-

proximately 32% reduction in plasma renin activity, nitroprusside-induced hypotension was accompanied by a moderate 48% increase in plasma renin activity (from 9.4 ± 4.1 to 13.4 ± 7.1 ng·mL⁻¹·h⁻¹; P < 0.05), and the hypotension induced by high-dose isoflurane was associated with the greatest increase in plasma renin activity, with levels increasing 126% (from 10.4 ± 8.2 to 23.0 ± 19.9 ng·mL⁻¹·h⁻¹; P < 0.05).

Cardiac filling pressures were unchanged with isoflurane. Both central venous and pulmonary capillary wedge pressures increased significantly with esmolol (52% and 23%, respectively). Although central venous pressure was unchanged with nitroprusside, there was a significant decrease in pulmonary capillary wedge pressure.

Discussion

Nitroprusside is probably the most commonly used drug for the provision of deliberate hypotension. Its popularity is related to its potency and short duration of action; however, certain limitations and risks are associated with its use. These include reflex tachycardia (3), tachyphylaxis (4), rebound hypertension (5), pulmonary shunting (6), and the potential for cyanide toxicity (7). Consequently, to minimize these concerns and to limit the total dose of nitroprusside administered, several adjunctive pharmacologic agents have been combined with nitroprusside. Among these agents are isoflurane, a potent inhalation anesthetic with vasodilating properties, and propranolol, a β -blocker that decreases baseline sympathetic tone and attenuates the stress response (8). Unlike isoflurane, which has been used as a primary agent for induced hypotension (9), β -blockers available before the release of esmolol had elimination half-lives that were too long for this use and thus served as secondary rather than primary hypotensive agents (8,10,11). Esmolol's elimination half-life of 9 min provides both ease in achieving the desired level of hypotension by regulating the dose and ease in terminating the hypotensive effect after the termination of the infusion. In contrast to isoflurane, esmolol administration can be continued in the intensive care unit should a reduction in blood pressure be indicated in the postoperative period, as is frequently the case after operation for AVM.

Although one patient was resistant to 4% isoflurane, all three agents were effective in providing 20% reduction in MAP. The hypotensive mechanism with nitroprusside and isoflurane is peripheral vasodilation, as demonstrated by a reduction in systemic

Table 2. Hemodynamic Variables Before and During Deliberate Hypotension

	Isoflurane	Nitroprusside	Esmolol
MAP (mm Hg)			
n	9	10	10
Control	82 ± 5	83 ± 5	82 ± 6
Hypotension	$64 \pm 4^{\circ}$	65 ± 4°	$65 \pm 6^{\circ}$
SBP (mm Hg)			
n	9	10	10
Control	105 ± 6	110 ± 6	106 ± 6
Hypotension	86 ± 6"	88 ± 7*	$82 \pm 6^{\circ}$
DBP (mm Hg)			
n	9	10	10
Control	66 ± 5	68 ± 5	69 ± 9
Hypotension	53 ± 4 "	54 ± 6°	54 ± 6^{a}
HR (beats/min)			
n	9	10	10
Control	83 ± 13	91 ± 23	88 ± 17
Hypotension	91 ± 20	$103 \pm 24^{\circ}$	67 ± 10°
CO (L/min)			
n	9	7	9
Control	6.2 ± 1.1	6.9 ± 1.9	6.2 ± 1.3
Hypotension	6.4 ± 2.2	7.6 ± 2.1	3.8 ± 0.8^{a}
CVP (mm Hg)			
n	9	7	9
Control	6 ± 4	6 ± 4	7 ± 3
Hypotension	7 ± 4	5 ± 2	10 ± 3°
PCWP (mm Hg)			
n	9	7	9
Control	10 ± 3	11 ± 3	10 ± 4
Hypotension	10 ± 4	8 ± 4°	12 ± 4^a
SVR (dyne·cm·s ⁻⁵)			
n	9	7	9
Control	1006 ± 215	956 ± 285	995 ± 201
Hypotension	779 ± 226"	681 ± 177°	1195 ± 275°
PRA $(ng \cdot mL^{-1} \cdot h^{-1})$			
n	8	8	8
Control	10.4 ± 8.2	9.4 ± 4.1	10.4 ± 9.0
Hypotension	23.0 ± 19.9°	13.4 ± 7.1^{a}	7.1 ± 7.4 "

CO, cardiac output; CVP, central venous pressure; DBP, diastolic blood pressure; HR, heart rate; MAP, mean arterial pressure; PRA, plasma renin activity; PCWP, pulmonary capillary wedge pressure; SBP, systolic blood pressure; SVR, systemic vascular resistance.

Values are mean ± sp.

vascular resistance with essentially no change in cardiac output. In contrast, the hypotensive effect of esmolol is due to a profound decrease in cardiac output that exceeds both the reductions in blood pressure and heart rate.

Plasma renin levels were found to increase with nitroprusside but even more so with isoflurane. Although Macnab et al. reported that nitroprusside-induced hypotension caused a greater increase in plasma renin activity than isoflurane-induced hypotension, their study differed in their use of supplemental fentanyl, of a higher isoflurane concentration at baseline, and of halothane rather than isoflurane in

the control group (12). As previously demonstrated with other β-blockers (2), esmolol is associated with a reduction in plasma renin activity. Despite this reduction in plasma renin activity, there is a significant reflex increase in systemic vascular resistance associated with esmolol-induced hypotension. This increase in afterload could potentially further compromise cardiac function especially in patients with limited myocardial reserve. As a result, the decrease in cardiac output may far exceed the decrease in MAP and may compromise organ perfusion. In 3 of 9 patients given esmolol in the present study, cardiac output decreased below 3.0 L/min during hypoten-

^{*}Significantly different from control levels during stable isoflurane anesthesia just before the initiation of hypotension.

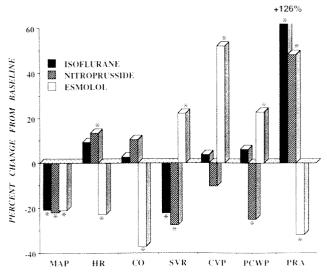


Figure 1. Percent changes from baseline in hemodynamic variables and plasma renin activity associated with hypotension induced by either esmelol, sodium nitroprusside, or high-dose isoflurane. For mean arterial pressure (MAP) and heart rate (HR), n=10 for esmolol and nitroprusside and n=9 for isoflurane. For cardiac output (CO), central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), and systemic vascular resistance (SVR), n=9 for esmolol and isoflurane and n=7 for nitroprusside. For plasma renin activity, n=8 in all groups. *Significantly different from other two groups.

sion. In each of these cases, cardiac output decreased by more than 50%. Conversely, the lowest cardiac outputs recorded in the nitroprusside and isoflurane groups were 5.1 and 4.3 L/min, respectively. Of note, there was a negative correlation between the dose of esmolol required to reach the end point of blood pressure in this study and the effect on cardiac function. Patients requiring smaller doses of esmolol to effect a 20% reduction in blood pressure had the greatest decreases in cardiac output, whereas patients who were somewhat resistant and who required larger esmolol doses had their cardiac output better maintained (Figure 2).

Esmolol may offer some advantages in terms of a favorable balance between myocardial oxygen supply and demand, whereas both isoflurane and nitroprusside have been implicated as precipitators of myocardial steal phenomenon. The decreased heart rate seen with esmolol use decreases metabolic demand, whereas the protracted diastolic time potentially increases blood supply to the myocardium. In addition, esmolol may offer a potential benefit over nitroprusside by preventing reflex tachycardia and rebound hypertension. The potential for esmolol-induced myocardial depression, however, is significant. Thus, caution must be exercised when considering the use of esmolol in patients with limited myocardial reserve. The magnitude of cardiac output depression

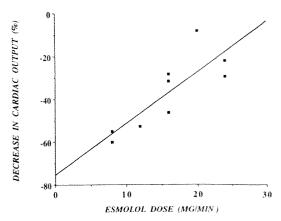


Figure 2. Correlation between esmolol dose required to obtain an approximately 20% reduction in MAP and the resultant reduction in cardiac output. (r = 0.83.)

seen in young healthy patients in this study might justify either pulmonary artery catheterization or the use of one of the newer noninvasive monitors of cardiac function in this clinical setting.

The present study did not examine the posthypotension period because it was frequently necessary to gradually increase MAP to assess and to treat bleeding from the AVM bed.

It is desirable to limit the number of drugs to which a patient is exposed in the course of an anesthetic. Occasionally, however, a combination of medications may be more efficacious or may provide a level of safety that may not be achieved with a single agent. Although the effectiveness of nitroprusside is rarely questioned, several adverse reactions have been attributed to its use. Esmolol, on the other hand, though effective as a sole agent for the induction of hypotension, may cause marked myocardial depression. Synergism has previously been demonstrated between nitroprusside and esmolol during both isoflurane (1) and nitrous oxide/narcotic anesthesia (13). Different hypotensive agents possess different pharmacologic properties that are desirable during induced hypotension. The combination of these agents may therefore provide a pharmacologic profile that is superior to either agent when given alone.

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Hemodilution During Bone Marrow Harvesting in Children

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Eight children (1-17 yr) underwent bone marrow harvesting while in cytostatic-induced remission of their disease (leukemia [n = 6], Ewing sarcoma, and non-Hodgkin lymphoma). After the induction of general anesthesia, all patients were loaded with 10 mL/kg of a 6% high-molecular dextran solution (Macrodex-Pharmacia), which resulted in a significant preoperative decrease in hematocrit (Hct) from 32% \pm 6% to 28% \pm 5% (hypervolemic hemodilution) and also allowed the procedure to be performed without systemic heparinization. The blood aspirated during the harvest (24 \pm 6 mL/kg; mean \pm sD) was replaced with a solution of 6% dextran and Ringer's acetate solution, and the Hct decreased from 28% \pm 5% to a minimum of 18% ± 3%. Immediately after the harvest, 10 mL/kg of homologous packed red blood cells was transfused, increasing Hct to 25% \pm 3%. Oxygen saturation in the superior caval vein (ScvO₂) decreased from 79% ± 4% before the harvest to 70% \pm 3% (P < 0.01) at the end of it, and then increased to 74% \pm 3% after the transfusion of homologous packed red blood cells. There was a strong linear correlation between mean values for Hct and ScvO2 during the various stages (r = 0.99). Mean heart rate decreased gradually during the procedure, from 106 ± 10 to 86 ± 7 beats/min. There was no significant change in arterial pressure, but cardiac output measured by impedance cardiography was about 30% greater during harvesting than during undisturbed anesthesia. Pulse oximetric saturation was 99% or 100% throughout. Caval venous blood lactate and pyruvate concentrations remained within normal limits in all children. Recovery after anesthesia was uneventful, except in one child in whom severe shivering developed. It is concluded that the hemodilution resulted in a statistically but not clinically significant decrease in Scvo2 that was well tolerated by the patients as judged from hemodynamic responses as well as levels of arterial oxygen saturation (SaO_2) and blood lactate.

Key Words: BLOOD, HEMODILUTION—bone marrow harvesting. ANESTHESIA, BONE MARROW HARVESTING.

Autologous bone marrow transplantation is the marrow rescue after high-dose cytotoxic chemotherapy or chemoradiotherapy by reinfusion of the patient's own marrow previously harvested and preserved. There are few reports (1–6) regarding the anesthetic management of patients undergoing bone marrow harvesting for posterior autografting and, to our knowledge, none that directly addresses the problems faced during the anesthesia of children undergoing this procedure. Among these are the potential threats of simultaneous hypovolemia and anemia that can be created by the aspiration of large amounts of bone marrow. Most commonly, homologous blood products are given to compensate for the blood loss

^{(1–3,5–6).} Alternatively, the harvested volume is limited to 10 mL/kg and the number of harvests is increased to assure the recovery of an adequate number of bone marrow cells. Intraoperative hemodilution is an established procedure to reduce the need for homologous blood transfusions that has been used successfully in children during orthopedic (7), open-heart (8), and cancer surgery (9). There are different approaches to induce hemodilution. We describe preoperative hypervolemic hemodilution (the reduction in hematocrit [Hct] induced by expansion of the plasma volume) followed by additional hemodilution during the harvest of bone marrow by substituting blood losses with cell-free fluids. To assess how the children tolerated the procedure, hemoglobin concentration (Hb), Hct, and superior caval venous oxygen saturation (Scvo₂) were measured as were hemodynamic responses and blood lactate and pyruvate concentrations.

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Table 1. Demographic Data and Diagnoses

			-			
Patient	Sex	Age (yr)	Weight (kg)	Diagnosis		
1	F	6	27	ALL, CR—3		
2	F	15	59	ES, CR-1		
3	M	10	30	ALL, CR—2		
4	F	17	52	AML, CR-1		
5	M	10	39	NHL, SR		
6	F	11	43	ALL, CR—2		
7	F	11	39	ALL, CR—3		
8	M	1	12.5	AML, CR-1		

ALL, acute lymphoblastic leukemia; AML, acute myeloblastic leukemia; NHL, non-Hodgkin lymphoma; ES, Ewing sarcoma; CR, complete remission—number of remissions; SR, sensitive relapse.

Methods

Eight children previously treated with cytostatic drugs for various malignancies were studied after obtaining institutional ethical committee approval and informed consent from the parents. Individual patient's data and diagnoses are presented in Table 1. In each patient, a tunneled central venous catheter had been previously inserted for chemotherapy. Catheter tip positioning in the superior caval vein was confirmed by fluoroscopy or chest x-ray. Rectal midazolam (0.3 mg/kg, maximum 7.5 mg) and atropine (0.02 mg/kg, maximum 0.5 mg) were administered about 15 min before intravenous anesthesia induction with 4-8 mg/kg thiopental and 0.5 mg/kg meperidine. Orotracheal intubation was facilitated with 0.1 mg/kg vecuronium. Anesthesia was maintained with isoflurane (0.75% inspired concentration), nitrous oxide in oxygen (70%:30%) and intermittent doses of vecuronium. Volume-controlled ventilation was performed with a Servo Ventilator 900 C (Siemens-Elema). Positive end-expiratory pressure (3–5 cm H_2O) was applied. End-tidal Pco_2 , as measured with a Siemens-Elema CO₂-analyzer 930, was held between 3.5 and 4.5 kPa (26 and 33 mm Hg). The CO₂ excretion rate, displayed on the analyzer, was recorded. The patients were placed in the prone position and a caudal block with plain 0.25% bupivacaine (0.5 mL/kg) was performed. A basal infusion of 2.5% glucose in half normal saline (Rehydrex, Pharmacia) (5 mL·kg $^{-1}$ ·h $^{-1}$) was started.

The probe of a pulse oximeter (Nellcor 100) was attached around a finger for continuous measurement of arterial oxygen saturation and heart rate. Central venous pressure (CVP) was measured with a Hewlett-Packard transducer and esophageal temperature with an electronic thermometer. The cuff of a Dinamap (Critikon) oscillometric pressure monitor

was wrapped around an upper arm to intermittently obtain mean, systolic, and diastolic arterial pressures. An impedance cardiograph (NCCOM3, Bomed Medical) was used to measure cardiac output (CO). Body surface area (BSA) derived from height and weight (10) was used to calculate cardiac index (CI) from the following formula: CI = CO/BSA.

Superior caval venous oxygen saturation was measured by analyzing blood samples on an OSM2 oxygen saturation meter (Radiometer). Caval venous Hb and Hct were obtained on a Hemocue apparatus (LED Diagnostics) and a microhematocrit centrifuge (Hettich), respectively. Blood samples obtained during stages 1, 5, and 6 (see below) were immediately frozen in liquid nitrogen for later measurement of lactate and pyruvate concentrations by a specific enzymatic fluorometric technique according to Lowry (11).

Baseline measurements during undisturbed anesthesia (stage 1) were followed by the administration of 0.3 mL/kg of a low-molecular dextran preparation (Promiten, Pharmacia) and subsequent infusion of a 6% dextran 70 solution in isotonic saline (Macrodex, Pharmacia), 10 mL/kg. The dextran infusion had the double objective of inducing mild anticoagulation, which was believed to facilitate the harvesting, and of obtaining a hypervolemic state that resulted in a significant decrease in Hct and created a margin for subsequent blood volume loss. Thereafter, a new set of measurements was performed (stage 2). Bone marrow aspiration from the iliac crest was then started without systemic heparinization. The blood loss was compensated for by infusing a further 0.5 mL of 6% dextran 70 and 1 mL of Ringer-acetate for each milliliter harvested. Measurements were repeated when 10 and 20 mL/kg had been aspirated (stages 3 and 4), at the end of harvesting (stage 5), and after infusing 10 mL/kg of homologous packed red blood cells (HRBC) (stage 6). The Hct of the HRBC was about 60%. The harvested marrow was cryopreserved upon separation of mononuclear cells. The anesthesia was terminated and the patient was transferred to the postoperative ward. The plasma and red blood cell fraction recovered after processing was resuspended with normal saline solution to a Hct of 55%-60% and reinfused 2-5 h after harvest (5-10 mL/kg).

Baseline data were compared with subsequent values with the two-sided Student's *t*-test for paired data. *P*-values below 0.05 were considered significant. Linear regression analysis was used to investigate the relationship between Hct and Scvo₂.

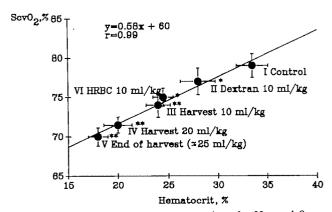


Figure 1. Relationship between mean values for Hct and Scvo₂. The bars show the standard error. Significant change in Scvo₂ in relation to stage 1 (*P < 0.05 and **P < 0.01, respectively). All changes in Hct were statistically significant (P < 0.01).

Results

Anesthesia lasted 129 \pm 30 min (mean \pm sp). The harvested volume was 24 ± 6 mL/kg (range, 18-38 mL/kg). Mean ETco₂ during the different stages was 3.9-4.2 kPa (29-31 mm Hg) with an sp of 0.4-0.5 kPa (3-4 mm Hg). Mean CO₂ excretion rate varied between 128 and 146 mL/min with an sp of 37-50 mL/min. Changes in CO₂ excretion were not significant. Sao₂ was 99% or 100% in all patients during all stages. Esophageal temperature decreased gradually from $36.8 \pm 0.5^{\circ}$ C during stage 1 to $35.2 \pm$ 0.8° C during stage 6 (P < 0.05). The immediate postoperative period was uneventful except that severe shivering developed in one child after anesthesia and required supplemental oxygen to maintain a normal Sao₂. There was no postoperative fever and all patients were discharged within 1 wk.

Hemoglobin Concentration, Hematocrit, and Central Venous Oxygen Saturation

Initial (stage 1) Hct and Hb were $32\% \pm 6\%$ (range, 24%-38%) and 113 ± 20 g/L (range, 83-138 g/L), respectively, decreasing to $28\% \pm 5\%$ (range, 19%-33%) and 88 ± 8 g/L (range, 75-98 g/L) after the infusion of dextran solution. The Hct and Hb then decreased progressively during the harvest to $18\% \pm 3\%$ (range, 15%-23%) and 64 ± 8 g/L (range, 53-77 g/L) at the end of it (Figure 1). After transfusing 10 mL/kg of HRBC the Hct was $25\% \pm 3\%$ (range, 23%-29%) and Hb 82 ± 3 g/L (range, 80-86 g/L). Hematocrit and Hb 1 h after postoperative retransfusion of the plasma and red cell fraction of the harvest were, respectively, $31\% \pm 3\%$ (range, 28%-35%) and 108 ± 14 g/L (range, 97-139 g/L). During harvesting,

central venous oxygen saturation decreased with decreasing Hct and there was a strong linear correlation between mean Scvo₂ and mean Hct over the various stages (Figure 1). The median for the corresponding correlation coefficients in individual patients was 0.88 (range, 0.30–0.96). The two lowest individual values for Hct at the end of harvesting were both 15% (patients 5 and 6) and Scvo₂ was, respectively, 74% and 71% in these patients. The lowest observed Scvo₂ (65%) was in patient 1 who had a minimum Hct of 18%.

Hemodynamics

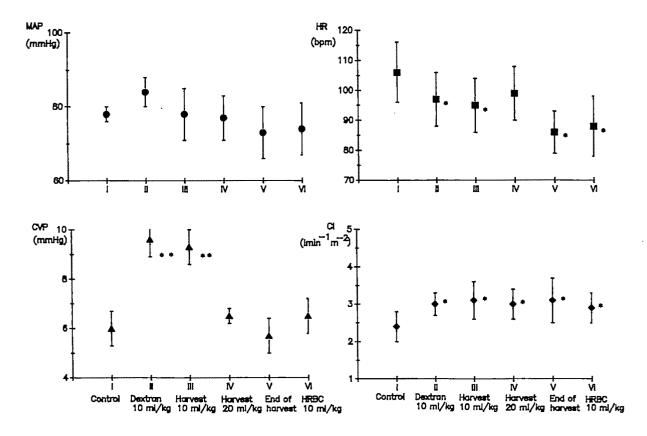
Mean systolic and diastolic arterial pressures ranged between 101 and 106 mm Hg and between 55 and 67 mm Hg, respectively, with an sp of 19–17 mm Hg for systolic arterial pressure and 7–9 mm Hg for diastolic arterial pressure. These changes were not significant, neither were those in mean arterial pressure (Figure 2). Heart rate was higher during the control stage than subsequently (Figure 2). There was an increase in CVP from 6 ± 2 to 10 ± 2 mm Hg between stages 1 and 2, i.e., after infusing 10 mL/kg of dextran solution before harvesting (Figure 2). Cardiac index increased significantly after this infusion, and remained higher than the control value until the end of harvesting (Figure 2).

Lactate and Pyruvate Concentrations

Venous lactate concentration was 1.2 ± 0.2 mmol/L during stage 1, 1.5 ± 0.4 mmol/L during stage 5 (not a significant difference), and 1.6 ± 0.4 mmol/L during stage 6 (P < 0.05 vs stage 1), both values being within the normal range (12,13) in all patients. In patient 3, who had the highest value (2.10 mmol/L) during stage 6 and the largest relative increase (90%) in lactate concentration between stages 1 and 6, the minimum observed Hct was 20%. Mean pyruvate concentrations were 0.06, 0.08, and 0.07 mmol/L during stages 1, 5, and 6, respectively, with an sp of 0.01 mmol/L throughout.

Discussion

The risks of transmitting disease and compromising immune defenses (14–16) combine to make it desirable to avoid transfusion of homologous blood. To achieve this, adults may predonate blood a few weeks before procedures with anticipated blood loss,



<u>Figure 2</u>. Hemodynamics. Values are mean \pm se. Significant change in relation to stage 1 (*P < 0.05 and **P < 0.01, respectively).

but this is often impractical in children, in whom preoperative and/or intraoperative hemodilution are the elected methods for reducing the need of donor blood in procedures involving substantial blood loss. Previous studies have shown that a reduction of Hct to about 20% is well tolerated (7–9,17–20).

There were three reasons why we used high molecular dextran: (a) it served as a plasma expander in stage 1 decreasing the Hct by hypervolemic hemodilution, (b) its mild anticoagulant properties facilitated the harvesting, so that systemic heparinization (21) was not needed, and (c) it was used as a plasma substitute combined with Ringer's acetate solution. The patients were pretreated with low-molecular dextran with a mean molecular weight of 1000 (Promiten, Pharmacia) before being given the highmolecular dextran solution (hapten inhibition). In adults, this reduces the risk of severe anaphylactic reactions to dextran to 0.008% (22). We gave 1-1.2 g/kg of dextran 70. The suggested maximum dose is 1.5 g/kg of dextran 70, below which dose bleeding problems are seldom seen (23). Volume replacement was performed with approximately equal proportions

of 6% dextran and Ringer's acetate, at total volumes exceeding those aspirated from the iliac crest by more than 10 mL/kg. A 3% dextran solution has been reported to give an approximately isovolemic plasma expansion (24), which means that blood volume was probably well maintained in our patients. This is also suggested by the stable arterial pressure, the decreasing heart rate during the procedure, and the unchanged or even increased CVP. Cardiac output increased about 25% after the initial plasma volume expansion obtained with the infusion of 10 mL/kg of dextran. The subsequent maintenance of CO around this level in spite of the return of CVP to control values suggests that anemia also contributed to the increase in CO. A word of caution is necessary, however, regarding the CO data obtained with the NCCOM3 impedance cardiograph, because the method has been reported to agree poorly (25) with thermodilution. Because some authors state that trends are adequately represented by the device (26–28), we considered it worthwhile to report the CO measurements in spite of these reservations.

Ideally, mixed venous oxygen content is needed for a reliable estimate of whole body oxygen extraction, but this requires pulmonary artery catheterization, which we considered too invasive. Instead, the saturation of superior caval venous blood was studied. Tahvanainen et al. (29) found a close correlation between the two measures, and, for the purpose of this discussion, we assume that the changes in superior caval venous saturation reflected those of mixed venous blood.

The decrease in mean Scvo2 from 79% to 70% during harvesting suggests that the reduction in oxygen carrying capacity of the blood with decreasing Hb was not fully compensated for by the increase in CO (30). Indeed, mean CO increased by only about 30% between stages 1 (control) and 5 (after harvesting), whereas the calculated mean arterial oxygen content (31) decreased by about 55%. If one assumes that oxygen consumption was constant, which is reasonable in view of the nearly unchanged CO₂ excretion rate, then CO would have had to increase in proportion to the decrease in oxygen-carrying capacity to assure that venous oxygen saturation was maintained. In the present study, mean Scvo₂ decreased in a nearly linear way with the Hct (Figure 1). This agrees with the findings of Wilkerson and coworkers who observed a linear increase in extraction ratio as Hct decreased to 10% (32,33). Our results contrast somewhat with other studies (reviewed in Reference 18) in which a decrease in mixed venous oxygen saturation was only seen when Hct decreased below 20%; we observed a statistically significant decrease in Scvo₂ even with small changes in Hct.

The hemodynamic stability, the maintained pulse oximetric saturation, and the fact that central venous concentrations of lactate and pyruvate remained within normal limits in all patients show that the procedure was well tolerated in spite of the statistically (but hardly clinically) significant reduction in Scvo₂. We conclude that a Hct of 15% is acceptable during a carefully controlled anesthetic, but are uncertain whether a child should be allowed to emerge from anesthesia with this degree of anemia. The tolerance margins to tissue hypoxia could be unacceptably narrow with such a low oxygen carrying capacity in an awake, active child. This was the main concern that made us transfuse HRBC toward the end of the anesthetic in spite of the hemodynamic and metabolic stability at this point. However, we think that one could modify the technique to manage safely the same amount of blood loss entirely without homologous blood products, provided the child does not have cardiovascular or lung disease. One could, for example, combine intraoperative hemodilution and preoperative hemodilution, with blood collected immediately before the harvesting and reinfused toward the end of the procedure.

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An Alternative Strategy for Infection Control of Anesthesia Breathing Circuits: A Laboratory Assessment of the Pall HME Filter

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BERRY AJ, NOLTE FS. An alternative strategy for infection control of anesthesia breathing circuits: a laboratory assessment of the Pall HME Filter. Anesth Analg 1991;72:651–5.

Contaminated breathing systems have been responsible for nosocomial upper respiratory tract and pulmonary infections in patients undergoing general anesthesia. The current infection control guidelines for anesthesia breathing circuits require single-patient use or high-level disinfection of breathing tubes, y-connector, and reservoir bag. An alternative infection control strategy has been suggested that incorporates placement of a microbial filter downstream from the y-connector between the circuit and the patient. This laboratory study assessed the capacity of the Pall HME Filter as a bidirectional barrier to transmission of bacteria

between the y-connector of an anesthesia circle breathing system and a test lung. The investigators modified a sterile circle system to allow aerosolization of a suspension of 10^9 Micrococcus luteus over 5 h into the inspiratory limb proximal to the y-connector or downstream from the filter into the test lung. Cultures indicated that the Pall HME Filter placed between the y-connector and the test lung completely prevented transmission of bacteria in both directions. The results of this study suggest that the Pall HME Filter could be used as an effective microbial barrier between the anesthesia circle breathing system and the patient as part of an alternative strategy for infection control.

Key Words: EQUIPMENT, ANESTHESIA CIRCUITS—filters. INFECTION, PREVENTION—anesthesia circuit filters.

Contaminated anesthesia breathing circuits have been implicated as the cause of significant and often fatal pulmonary and respiratory tract infections in patients undergoing general anesthesia (1). In one report, an outbreak of *Pseudomonas aeruginosa* infection was terminated by sterilizing the reusable face mask, y-connector, and breathing tubes from the contaminated machine, and by instituting disinfection of these pieces after each use. Routine singlepatient use of disposable circuit hoses, y-connector, and face mask, or high-level disinfection of reusables between patients, is the currently recommended infection control standard in the United States (2,3). This policy appears to be effective in preventing nosocomial respiratory tract infections associated with anesthesia equipment (2-5).

European clinician-investigators have advocated an alternative infection control strategy for the anesthesia breathing circuit that incorporates the use of a new Pall HME Filter with each patient (6,7). The Pall HME Filter (Pall Biomedical Products Corporation, Glen Cove, N.Y.) is an effective heat and moisture exchanger (8), but additionally functions as a bacterial (9) and viral (10) filter in short-term tests conducted by the Pall Corporation. If this device prevented bidirectional transmission of infectious pathogens for a prolonged period, it could be placed between the patient's airway and y-connector of the circle system and would provide a microbial barrier between the patient and anesthesia machine. The proposed infection control strategy requires only that a new Pall HME Filter be used with all patients undergoing general anesthesia and would permit reuse of the anesthesia circle breathing tubing, y-connector, reservoir bag, and ventilator bellows and tubing. This would have several benefits, including a substantial cost savings for equipment and labor and a reduction in volume of waste from disposable equipment. The current study is designed to assess this alternative infection control strategy by testing the effectiveness of the Pall HME Filter in completely removing bacte-

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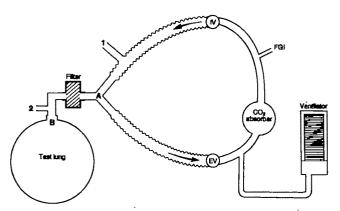


Figure 1. Anesthesia circle breathing system and ventilator modified for this study for aerosolization of bacteria. The Pall HME Filter (Filter) is positioned in the breathing circuit in this figure as in trials 3 and 4. Sites for introducing aerosolized bacteria into the system are indicated as 1 and 2. Sites that are cultured are labeled A and B. IV, inspiratory valve; EV, expiratory valve; FGI, fresh gas inflow

ria when used in an anesthesia circle system under simulated clinical conditions.

Methods

A standard anesthesia circle system attached to a pneumatically driven volume ventilator was modified to allow aerosolization of bacteria either into the inspiratory breathing tube proximal to the y-connector (site 1) or at the right angle connector (site 2) proximal to a test lung (a 3-L reservoir bag) (Figure 1). A sterile DeVilbiss Glass Nebulizer 40 (the DeVilbiss Company, Sumerset, Pa.) attached to a source of filtered, compressed air was used to aerosolize a suspension of Micrococcus luteus through latex tubing (inner diameter 5/8 in) at site 1 or 2. For each part of this study, new inspiratory and expiratory breathing tubes, y-connector, right angle connector, and test lung were sterilized using ethylene oxide. The setup and duration of the four trials in this study are outlined in Table 1. Trials 1 and 2 were designed to ensure that aerosolization of bacteria at either site 1 or 2 would result in contamination of the breathing circuit at both culture sites A and B (Figure 1) when the Pall HME Filter was not used. For each trial, 108 Micrococcus luteus organisms suspended in 5 mL of normal saline were aerosolized over 15 min. During all trials, the fresh gas flow into the circle system consisted of 2 L/min of oxygen, and the ventilator was set to deliver a tidal volume of 600 mL at a rate of eight per minute.

Trials 3 and 4 tested the efficacy of the Pall HME Filter as a microbial barrier for the 5-h duration of each test. At half-hour intervals, 10⁸ Micrococcus luteus

organisms were aerosolized at the sites indicated in Table 1, and cultures were taken at sites A and B after each hour. After culturing, either a sterile test lung, or sterile inspiratory and expiratory tubing and y-connector, were inserted as indicated in the protocol (Table 1). A single Pall HME Filter was used for the 5-h duration of trials 3 and 4. Each of the four trials was repeated once to ensure reproducibility of results.

For all portions of this study, cultures were taken at sites A and B by thoroughly sampling the inside of the breathing circuit using two swabs moistened with Trypticase soy broth (BBL, Cockeysville, Md.). The swabs were placed in the same broth medium and incubated for at least 48 h to assess growth. Any positive cultures were then subcultured to blood agar plates for identification of organisms.

Results

In both sets of trials 1 and 2, all cultures taken at sites A and B were positive for *Micrococcus luteus*, indicating effective contamination of these portions of the circle system by aerosolizing at either site 1 or 2. In both sets of trials 3 and 4, there were no positive bacterial cultures from samples taken distal to the Pall HME Filter. All cultures taken at sites proximal to the filter, on the side of aerosolization, were positive for *Micrococcus luteus*.

Discussion

The Pall HME Filter was specifically selected for use as part of this alternative infection control strategy for several reasons including its unique composition. The filtering material is a hydrophobic ceramic matrix that blocks particles that are the size of single viruses and does not permit passage of liquids. Particles in gases are retained by the filter by three mechanisms (10). Particles larger than 1 μ m are physically removed by direct interception with the presenting filter surface. Inertial impaction results in $0.5-1-\mu m$ particles colliding with the filter medium and being captured within its pores. Smaller particles undergo Brownian motion and are effectively retained by the filter membrane (diffusional interception). In previous studies performed by the manufacturer, the Pall HME Filter was shown to be effective in removing more than 99.999% of monodispersed bacteriophage MS-2 (0.02 μ m in size) (10).

The airborne transmission of respiratory-generated particles that carry viruses has been extensively

Table 1. Study Protocols

Trial	Site to aerosolize bacteria	Pall HME Filter	Trial duration (h) ^b	Comments
1	1	No	0.5	
2	. 2	No	0.5	
3	1	Yes	5.0	Sterile test lung and circuit elbow replaced at the end of each hour
4	2	Yes	5.0	Sterile inspiratory and expiratory tubing and y- piece replaced at the end of each hour

"See Figure 1 and text.

studied (11). Large particles produced by coughing rapidly settle and do not travel a great distance. Smaller particles, 1–3 μ m in size, are likely to contain fewer viruses but remain suspended in the atmosphere for a longer time and therefore can be widely disseminated by air currents. Because biologic aerosols are hygroscopic, the hydrophobicity of the Pall HME Filter contributes to the retention of respiratorytransmitted pathogens. Thus, the ceramic matrix of the Pall HME Filter prevents transmission of viruses both by its hydrophobicity and its ability to capture particles of various sizes. Although there has been an interest in a specific infection control protocol to prevent viral contamination of anesthesia breathing circuits used on patients carrying viruses such as the human immunodeficiency virus, isolation of viruses from respiratory equipment has not been described

In the clinical simulation in the present study, the Pall HME Filter was effective in preventing bidirectional transmission of a massive bacterial challenge. When 10⁹ Micrococcus luteus were aerosolized into the test system over 5 h, the Pall HME Filter effectively blocked the flow of the bacteria in both directions. Micrococcus luteus was selected as a test organism because its characteristic color makes it easy to identify in cultures. The bacterial load used in this study was a significantly greater challenge to the filter than would be expected in routine clinical use. Shiotani et al. measured 0.64 ± 0.38 organisms emitted per minute of anesthesia in the expired gases of 15 intubated patients (13). Therefore, the capacity of the Pall HME Filter provides an adequate margin of reserve for extreme cases of contamination for at least 5 h. Quantitative cultures were not performed in the current study because transmission of any organisms across the filter would be unacceptable in clinical practice. Each filter is individually quality-tested for retention effectiveness by the Pall Corporation. Because of the 100% quality control by the manufacturer, we chose to use only duplicate trials of each protocol in the present study.

Several bacterial filters for use on the inspiratory or expiratory ports of the anesthesia circle breathing system have been developed (13,14). In previous clinical practice, bacterial filters were placed either distal to the inspiratory valve or proximal to the expiratory valve, or at both locations, in an attempt to prevent transmission of organisms from the nonremovable portion of the circle system to the patient, or vice versa. Ping et al. showed that routine cleaning and sterilization of equipment controlled bacterial colonization, and stated that the use of bacterial filters in these positions was not justified (15). This was verified in at least one clinical study that demonstrated no reduction in the incidence of postoperative pneumonia when bacterial filters were used adjacent to both the inspiratory and expiratory valves (16). The authors concluded that the routine use of filters in these positions was unnecessary and resulted in a significant unjustified health-care expense.

In the present study, the Pall HME Filter was positioned downstream from the y-connector, between the circle system and the test lung. In this location, the filter prevented transmission of organisms bidirectionally, and therefore is a microbial barrier separating the patient's respiratory tract from the components of the anesthesia circle system and machine. Based on these results, an alternative strategy for infection control for anesthesia equipment as suggested by some clinicians (6,7) would incorporate the use of a new Pall HME Filter between the y-connector of the circle system and each patient. This would permit the reuse of the y-connector, breathing and ventilator tubing, reservoir bag, and respiratory monitor adapters for several patients before disposal or disinfection. This infection control strategy would have several advantages over the current guidelines: (a) it could be used with all patients regardless of their infection carrier status; (b) it would prevent transmission of infectious agents from the anesthesia breathing circuit to immunocompromised patients; (c) it would reduce the costs associated with infection control for anesthesia equipment; and (d) it would provide passive humidification of inspired anesthetic gases administered to all intubated patients (8,17).

Tuberculosis can be transmitted in respiratory secretions, but there are no studies on whether the disease can be spread via anesthesia equipment. The Centers for Disease Control has reported that from 1984 through 1988 the observed number of cases of

^b10⁸ Micrococcus luteus aerosolized every 0.5 h.

Table 2. Cost Analysis for One Operating Room for Breathing Circuits—Comparison of Infection Control Strategies^a

Circuit component	Cost/item, first case	Cost of items for two subsequent cases	Total cost of item for three cases
Current procedure			
Anesthesia circuit and ventilator tubing ^b	\$3.24	\$6.48	\$ 9.72
Humidifying filter ^b	\$2.61	\$5.22	\$ 7.83
Disinfection of mass spectrometer connector and line filter	\$1.00	\$2.00	\$ 3.00
Total cost—all items			\$20.55
Alternative strategy			
Anesthesia circuit and ventilator tubing ^b	\$3.24	\$0	\$ 3.24
Pall HME Filter ^b	\$3.75	\$7.50	\$11.25
Disinfection of mass spectrometer connector and filter	\$1.00	\$0	\$ 1.00
Total cost—all items			\$15.49

[&]quot;Assumes three cases requiring general anesthesia per day in an operating room.

tuberculosis in the United States did not decline at the rate expected, in part because of an increasing incidence in persons infected with HIV-1 (18). Patients with unsuspected tuberculosis may be hospitalized and require general anesthesia as part of the workup of their disease (19). Current infection control recommendations for anesthesia equipment do not specifically address organisms such as the tubercle bacillus that are transmitted via respiratory secretions. Routine use of an effective microbial barrier would prevent transmission of pathogens from unsuspected carriers to anesthetic equipment.

When using the Pall HME Filter as part of an infection control strategy, the components of the breathing circuit beyond the filter will not be contaminated by pathogens from the respiratory tract of the patient and therefore could be used multiple times without disinfection or disposal. This alternative strategy would be expected to reduce the costs associated with infection control. The analysis in Table 2 indicates that implementation of the proposed infection control procedure at the author's institution would result in a savings of \$5.06 per operating room per day when three general anesthetics were given. Assuming a facility with 14 operating rooms occupied 260 days per year, \$18,418 would be saved in equipment and processing costs annually. Personnel, waste disposal, and equipment storage expenditures would also be reduced but have not been included in these estimates.

Previous investigations have determined that the resistance to a gas flow of 50 L/min through the dry Pall HME Filter was 0.02 cm $H_2O/L\cdot min^{-1}$ and did not change significantly when the filter was wet (8). The resistance of the filter increased slightly from 1.6 to 1.7 cm $H_2O/L\cdot s^{-1}$ over 6 h in patients who required

mechanical ventilation (20). This resistance to airflow is minimal and would not compromise minute ventilation in spontaneously breathing, anesthetized patients (21).

In summary, this laboratory study demonstrates that the Pall HME Filter is an effective barrier in preventing the transmission of *Micrococcus luteus* in the circle breathing circuit. Based on this finding, an alternative strategy for infection control of anesthesia equipment using the Pall HME Filter has been proposed and advantages over the current guidelines suggested. It will be necessary to conduct a clinical trial with patients undergoing general anesthesia to determine whether the use of the Pall HME Filter in this way will be an acceptable method of preventing the acquisition of nosocomial infections from anesthesia equipment.

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^{*}Cost for item at author's institution; may vary by specific brand and/or distributor.

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Pentamorphone for Management of Postoperative Pain

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WONG HY, PARKER RK, FRAGEN R, WHITE PF. Pentamorphone for management of postoperative pain. Anesth Analg 1991;72:656–60.

The efficacy, duration, and safety of the synthetic opioid pentamorphone in the treatment of acute postoperative pain were evaluated in a randomized, double-blind study of 72 patients given 0.08, 0.16, or 0.24 μ g/kg of pentamorphone or a placebo intravenously in the recovery room after major abdominal or orthopedic surgery. Only patients given 0.24 μ g/kg of pentamorphone experienced decreased pain

intensity and increased sedation, both transient in duration. Although the two higher doses of pentamorphone delayed the patient's request for supplemental morphine, the total amount of morphine required within the first hour was not different between treatments. No acute cardiorespiratory changes were observed. Pentamorphone (0.08–0.24 µg/kg) was ineffective for treating acute postoperative pain after major surgery.

Key Words: ANALGESICS, PENTAMORPHONE. PAIN, POSTOPERATIVE—pentamorphone.

Pentamorphone (14- β -pentylaminomorphinone) is a synthetic derivative of morphine (Figure 1) (1). In one animal study, the ED₅₀ of pentamorphone for antinociceptive activity varied from 1.5 to 8 times that of fentanyl, whereas respiratory depression, rigidity, and catatonia were less marked (2). In human volunteers, 0.12–0.24 μ g/kg of pentamorphone given intravenously (IV) has been found to enhance tolerance of experimental pain with clinically acceptable side effects (3). Based on these data, a randomized, double-blind, placebo-controlled study was designed to evaluate the efficacy, safety, and duration of action of a single injection of pentamorphone in providing acute postoperative analgesia after major surgical procedures.

Methods

After obtaining written informed consent, 72 ASA physical status I or II patients undergoing major abdominal or orthopedic surgery were randomly assigned to one of four treatment groups according to a

double-blind protocol. The subjects were randomized to receive intravenously 0.08, 0.16, or 0.24 μ g/kg of pentamorphone or a placebo (control). Exclusionary criteria included a history of respiratory and neurologic disorders, allergic reactions to opioid analgesics, or chronic use of opioid compounds during the 2 wk before the study. The study was carried out at Northwestern University in Chicago, Illinois and Washington University in St. Louis, Missouri. The protocol was approved by the institutional review boards at both institutions.

Anesthesia consisted of premedication with 1–3 mg IV midazolam (or 2–5 mg IM), induction with 3–5 mg/kg of thiopental, and maintenance with 0.7%–1% isoflurane and 60%–70% nitrous oxide (N_2O) in oxygen. Forty percent of the subjects received 2.5 μ g/kg IV fentanyl immediately before induction of anesthesia. No other intraoperative opioids were used. Vecuronium was used for muscle relaxation and was reversed with neostigmine or edrophonium at the end of the procedure. Supplemental (40%) oxygen was administered via face mask during recovery from anesthesia.

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Protocol for Drug Administration

Before they underwent surgery, all patients were instructed on the use of a visual analog pain scale (VAS) and a verbal pain scale (VPS) (4).

When the patients were awake in the recovery

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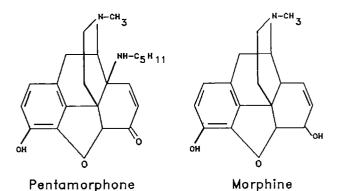


Figure 1. The chemical structure of pentamorphone (14-β-pentylaminomorphinone) and morphine.

room and complained of moderate-to-severe pain, the following baseline assessments were performed.

- Pain intensity was rated by the patients on the VPS as "none," "mild," "moderate," "severe," or "excruciating"; and on a 100-mm VAS, from 0 mm = "no pain" to 100 mm = "the worst pain ever experienced."
- 2. The level of sedation was assessed by a blinded observer using a four-point scale: (1) awake but nervous, (2) awake but calm, (3) asleep but easy to arouse, and (4) asleep and difficult to arouse.
- 3. Blood pressure, heart rate, respiratory rate, and arterial oxygen saturation by pulse oximetry (Spo₂) were measured.

When the patients rated their pain intensity as moderate or worse, one of the investigators not involved in the assessment process administered the assigned medication. The aforementioned assessments were then repeated 5, 10, 15, 30, and 60 min later.

Pain relief was defined as inadequate if the verbal pain scale was severe or excruciating after 10 min, and morphine sulfate in 2-mg increments was given intravenously to relieve pain. If pain relief was adequate, the patient was observed until an analgesic was requested. Upon request, morphine sulfate was administered in 2-mg increments. Results of VPS and VAS measurements made immediately before the first administration of morphine were recorded for all remaining evaluation times (5). The time to the first dose of morphine ($T_{\rm MOR}$) and the total amount of morphine administered in the first 60 minutes (M_{60}) were recorded.

Statistical Analysis

Demographic data, duration of anesthesia, time interval between the end of anesthesia and study

<u>Table 1</u>. Demographic Data and Analgesic Requirements in the Four Study Groups

	Dose	Dose of pentamorphone (µg/kg IV)					
	0	0.08	0.16	0.24			
Number (n)	18	19	18	17			
Age (yr)	42 ± 15	45 ± 15	42 ± 12	43 ± 10			
Weight (kg)	75 ± 13	75 ± 18	76 ± 14	65 ± 14			
Sex (M/F)	<i>7/</i> 11	3/16	<i>7/</i> 11	4/13			
T _{ANES} (min)	186 ± 86	158 ± 54	140 ± 71	170 ± 65			
T _{MED} (min)	30 ± 18	32 ± 17	20 ± 12ª	33 ± 12			
M ₆₀ (mg)	7.9 ± 4.0	7.1 ± 5.4	6.1 ± 4.4	3.9 ± 4.8			
T _{MOR} (min)							
Range	4-43	10-332	13 -9 1	17-227			
Median	14.5	19.0	29.5^{b}	35.0°			

 T_{ANES} , duration of anesthesia. T_{MED} , time between end of anesthesia and administration of test drug. M_{60} , total amount of morphine required in the first 60 min. T_{MOR} , time to the first dose of supplemental morphine.

Values are mean ± sp.

"Significantly different from the other three groups, P = 0.034.

Significantly different from placebo (control) group, P = 0.009. Significantly different from placebo (control) group, P = 0.0001.

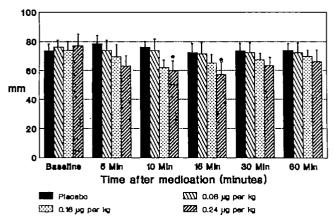
medication, and total amount of morphine (M_{60}) were analyzed with analysis of variance. Visual analog scale, VPS, level of sedation, and T_{MOR} were analyzed with Friedman two-way analysis of variance for within-group comparisons and with Kruskal-Wallis and Mann–Whitney U tests for between-group comparisons. Blood pressure, heart rate, and respiratory and blood oxygen saturation data were analyzed with multivariate analysis of variance with repeated measurements on one factor and t-tests. Statistical significance was defined as P < 0.05, with Bonferroni correction for multiple comparisons.

Results

The four groups of patients were similar with respect to age, sex, height, weight, duration of anesthesia, and time between end of anesthesia and administration of test drug (Table 1).

Pain Intensity

The VAS data showed a small but statistically significant decrease with time in the group receiving the highest dose of pentamorphone, 0.24 μ g/kg (P = 0.003) (Figure 2). In contrast, the VPS scores did not change with time in any group (Table 2). Betweengroup comparison of VAS and VPS at each evaluation time also showed no significant difference among the three doses, or between each dose and the placebo.



<u>Figure 2</u>. The change in pain intensity after IV administration of study medication or placebo as measured by VAS. VAS scores are on y-axis. Values are mean \pm sem. *Significant difference from baseline, P=0.0031.

<u>Table 2</u>. Verbal Pain Scores^a After Intravenous Administration of Pentamorphone or Placebo

		-						
		Time after medication (min)						
Dosage	0	5	10	15	30	60		
Placebo								
Range	(2,5)	(2,5)	(2,5)	(2,5)	(2,5)	(2,5)		
Median	4	4	4	4	4	4		
Mode	4	4	4	4	4	4		
Pentamorphone								
0.08 μg/kg								
Range	(2,5)	(2,5)	(2,5)	(2,5)	(2,5)	(2,5)		
Median	. 4	3	3	3	3	`3		
Mode	4	3	3	3	3	3		
0.16 μg/kg								
Range	(2,4)	(1,4)	(2,4)	(2,4)	(2,4)	(3,4)		
Median	3	3	3	3	3	3		
Mode	3	3	3	3	3	3		
0.24 μg/kg								
Range	(3,5)	(1,5)	(2,4)	(1,5)	(2,5)	(2,5)		
Median	4	3	3	3	3	`3´		
Mode	4	3	3	4	4	4		

[&]quot;Range (,)" denotes the minimum and maximum values of the range.

"Verbal pain scale: 1 = none, 2 = mild, 3 = moderate, 4 = severe, 5 = excruciating.

Time to First Dose of Morphine

 $T_{\rm MOR}$ ranged from 4 to 332 min. Most $T_{\rm MOR}$ values were less than 100 min but one patient who received 0.08 $\mu g/kg$ of pentamorphone had a $T_{\rm MOR}$ of 332 min and five patients who received 0.24 $\mu g/kg$ had a $T_{\rm MOR}$ longer than 100 min. The four groups were significantly different (P=0.001) even if $T_{\rm MOR}$ values greater than 100 min were excluded from analysis (P=0.01). The groups that received 0.16 and 0.24 $\mu g/kg$ of pentamorphone had longer $T_{\rm MOR}$ than the control group (P=0.009 and 0.0001, respective-

<u>Table 3</u>. Effect of Intraoperative Fentanyl on the Postoperative Analgesic Requirement^e

	Dose of pentamorphone (µg/kg IV)				
	0	0.08	0.16	0.24	
Number (n)					
Fentanyl (2.5 µg/kg)	7	8	7	6	
No fentanyl	11	11	11	11	
T _{MED} (min)					
Fentanyl (2.5 μg/kg)	31 ± 16	35 ± 14	22 ± 17	32 ± 6	
No fentanyl	29 ± 17	30 ± 18	18 ± 9	34 ± 14	
T _{MOR} (min)					
Fentanyl (2.5 μg/kg)	26 ± 14	27 ± 17	37 ± 28	51 ± 45	
No fentanyl	14 ± 4	53 ± 95	31 ± 16	73 ± 65	
M ₆₀ (mg)					
Fentanyl (2.5 μg/kg)	6.6 ± 5.1	5.1 ± 3.5	5.4 ± 3.9	3.0 ± 2.0	
No fentanyl	8.8 ± 3.1	8.5 ± 6.2	6.5 ± 4.8	4.4 ± 5.8	

Values are mean ± sp.

ly), but no significant differences were noted among the three doses.

Total Amount of Morphine in the First Hour

Although there was a trend for decreased morphine requirement with increasing doses of pentamorphone, the differences between the placebo group and the three groups receiving pentamorphone were not statistically significant. In addition, the intraoperative administration of 2.5 μ g/kg IV fentanyl did not delay the request for pain relief or the requirement for supplemental morphine (T_{MOR}), nor did it affect the amount of morphine required in the first 60 min after the operation (Table 3).

Level of Sedation

Within each treatment group, there was no significant change in the degree of sedation over time (Table 4). However, between-group comparisons showed that the group receiving 0.24 μ g/kg of pentamorphone was more sedated than the placebo group at 5 and 10 min after study drug administration. (With P values equal to 0.0002 and 0.004, respectively.)

Vital Signs

No statistically significant changes in blood pressure, heart rate, respiratory rate, or pulse oximetry occurred in the four treatment groups.

[&]quot;No significant differences were noted between fentanyl and no-fentanyl groups in any of the categories studied.

<u>Table 4</u>. Level of Sedation^a After Intravenous Administration of Drug or Placebo

		Time after medication (min)					
	0	5	10	15	30	60	
Placebo		7					
Range	1-4	1–3	1-3	1-3	1-4	2-4	
Mode	1	3	3	3	3	3	
Pentamorphone							
0.08 μg/kg							
Range	1–3	1-4	1-4	1-4	1-3	1-4	
Mode	2	3	3	3	3	3	
0.16 μg/kg							
Range	1-3	1-4	2-3	2–3	1-3	2-3	
Mode	2	3	3	3	3	3	
0.24 μg/kg							
Range	1-3	2-4 ^b	1-4°	1-4	1-4	1-3	
Mode	3	3	3	3	3	3	

*Sedation level: 1 = awake but nervous; 2 = awake but calm; 3 = asleep but easily arousable; 4 = asleep and difficult to arouse.

Side Effects

Two patients given $0.08~\mu g/kg$ of pentamorphone and one patient given $0.16~\mu g/kg$ had postoperative nausea and vomiting. There were no other opioid-related side effects.

Discussion

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The efficacy of pentamorphone in relieving postoperative pain was assessed in terms of the change in pain intensity after medication, the time interval before additional analgesic medication was required, and the total dose of supplemental analgesic required in the first hour. The results indicate that 0.08–0.24 μ g/kg of pentamorphone was of limited effectiveness in relieving postoperative pain after major surgery. In the group receiving 0.24 μ g/kg, a small but short-lived decrease in the VAS score was noted. However, there was no improvement in the clinical pain intensity rating. Although 0.16 and 0.24 μ g/kg of pentamorphone prolonged the time to supplemental analgesic administration, the "opioid-sparing" effect was minimal.

This investigation serves to emphasize the difficulty in extrapolating data from laboratory studies of pain to clinical practice. The pentamorphone dosage range chosen for this study was based on the report by Glass et al. (3) using increase in tolerance to experimental pain in human volunteers as an indicator of analgesic activity. They postulated that the therapeutic analgesic dose of pentamorphone is between the ED₅₀ for a 20% increase and the ED₅₀ for a 70% increase in pain tolerance, and arrived at a range of from 0.05 to 0.2 μ g/kg. There are several possible explanations for the failure of these pentamorphone dosages to provide postoperative pain relief. First, the postsurgical patients in this study and the volunteer subjects in the previous investigation represent different populations. However, one might expect the patients in our study to be more "sensitive" to opioid analgesics as they were older and in poorer health. Second, the methods used for assessing pain relief in our study are highly subjective. Third, the characteristics, severity, and impact of clinical pain after major operations were likely to exceed the experimental pain used in laboratory studies. Finally, the experimental pain stimulus was applied intermittently whereas surgical (incisional) pain is fairly constant.

In this study about 40% of patients received fentanyl at the time of induction of anesthesia (maximum, 2.5 μ g/kg). This small dose of fentanyl did not delay the request for analgesic after surgery, prolong the time to supplemental morphine, or decrease the total amount of supplemental morphine required (Table 3). When the patients who received intraoperative fentanyl were analyzed separately for the change in pain intensity, the results were identical to those obtained for the group as a whole. Thus, the intraoperative administration of 2.0–2.5 μ g/kg of fentanyl did not affect the conclusions drawn from this study.

Pentamorphone (0.08–0.24 μ g/kg) did not have adverse clinical effects on blood pressure, heart rate, respiratory rate, or oxygen saturation, in keeping with the published reports in human volunteers (3). Only patients in the group receiving 0.24 μ g/kg showed transient, statistically significant increases in sedation level. Whereas Glass et al. (3) reported dose-related respiratory depression, with apnea occurring in one subject receiving 0.24 μ g/kg and two subjects receiving 0.48 μ g/kg, this was not seen in our clinical study. Perhaps patients in our investigation experienced more severe pain that tended to counteract the respiratory depression observed in the volunteer study.

In conclusion, 0.08–0.24 μ g/kg of pentamorphone is ineffective in relieving acute pain after major abdominal or orthopedic operations. Although the highest dose of pentamorphone (0.24 μ g/kg) produced a transient decrease in pain intensity, it would appear to be of limited value in the early postoperative period. To determine the potential clinical role of this new analgesic, higher doses would be required to define its risk-to-benefit ratio. Future clinical investi-

Significant difference from placebo group (P = 0.0002). Significant difference from placebo group (P = 0.004).

gations involving larger doses of pentamorphone are needed to evaluate its analgesic potential and safety.

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Alcohol After Midazolam Sedation: Does It Really Matter?

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Patients who arrive home several hours after ambulatory surgery may drink alcohol. The extent to which the residual effects of drugs used in ambulatory surgery interact with alcohol, perhaps potentiating alcohol effects, is not known. Accordingly, the purpose of this study was to determine whether intravenous midazolam had residual effects that would interact with alcohol consumed 4 h after the midazolam injection. Healthy male volunteers (n = 16) participated in a double-blind, randomized, placebo-controlled crossover trial. Subjects were studied four times successively with 1 wk between trials. On each test day the subjects randomly received by slow intravenous injection (30 s) either saline or 0.1 mg/kg of midazolam. Four hours after injection, the subjects consumed a beverage that either

did or did not contain 0.7 g/kg of alcohol. Before and 1, 3, 5, and 7 h after injection (and before and 1 and 3 h after beverage consumption), psychomotor performance and mood were assessed. Whereas both midazolam and alcohol alone had effects on the dependent measures in this study, there were no significant interactions between the two drugs (i.e., potentiation of alcohol effects by midazolam or potentiation of midazolam by alcohol). We conclude that the effects of a short-acting benzodiazepine used in ambulatory surgery have probably dissipated by the time a patient arrives home, and that effects from alcohol ingested at home will probably not be influenced by the recent administration of a short-acting benzodiazepine such as midazolam.

Key Words: HYPNOTICS, BENZODIAZEPINES—midazolam. ALCOHOL, INTERACTION WITH BENZODIAZEPINES. ANESTHESIA, OUTPATIENT—midazolam-alcohol interaction.

Little is known about the postprocedure habits of ambulatory patients after discharge from surgical centers. A survey conducted more than 18 yr ago revealed that within 24 h of ambulatory surgery, despite being told not to, 73% of respondents who owned a car drove (1). The survey also revealed that 6% of the respondents ingested alcohol within 24 h after their surgery.

Given that a majority of people may drive within 24 h after ambulatory surgery and that some of these people may also drink alcohol, it is important to understand the residual effects of drugs commonly used in ambulatory surgery or endoscopy and the extent to which these residual effects interact with alcohol. If patients after ambulatory surgical proce-

dures drink alcohol after they have been discharged, it is possible that the risk of harm to themselves or others would be even greater than the risk from alcohol alone because the residual effects of the central nervous system-depressant drugs used in ambulatory surgery may potentiate the psychomotor effects of alcohol. Indeed, there are numerous studies demonstrating that the psychomotor-impairing effects of alcohol are potentiated by benzodiazepines (2–7). However, there are no studies that have examined the interaction between alcohol and benzodiazepines using a time frame in which alcohol use follows benzodiazepine administration by several hours. Such a study would be important from a clinical standpoint because this would mimic a scenario in which a patient after arriving home several hours following ambulatory surgery consumes alcohol. In the present study, healthy volunteers were given intravenous injections of either midazolam or placebo, and then 4 h later consumed a beverage that either did or did not contain alcohol. Psychomotor and cognitive functioning was assessed before and after midazolam and alcohol administration. This

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protocol assays independent effects of each drug and determines if alcohol effects are potentiated by administration of midazolam using a time-course similar to that of a patient drinking alcohol upon arriving home after outpatient surgery.

Methods

In this study, 16 healthy men (mean age, 23.6 \pm 3.1 yr; mean weight, 68.1 ± 10.1 kg) with a history of recreational alcohol use served as subjects. The study was approved by our institutional review board. An anesthesiologist took a history and performed a physical examination to determine the suitability of subjects for the study. Excluded from this study were persons who had an adverse experience with alcohol, general or intravenous anesthesia, or sedation/ analgesia previously, or in whom contraindications became apparent after physical examination. Persons accepted into the study also could not take prescription or recreational drugs (excluding alcohol) or overthe-counter medication during the 3 wk of the study. Informed written consent was obtained from subjects before the first session. On testing days, subjects were not allowed to eat or drink before the tests (i.e., neither overnight drinking nor eating). Subjects were instructed to refrain from drinking alcohol for 24 h before sessions. Alcohol abstinence was verified by measuring the blood alcohol level when subjects arrived for the session. Subjects were told not to drive a car, operate heavy machinery, or cook until the day after the study and were required to have an escort accompany them home after sessions. Subjects were paid for their participation upon completion of the study.

The study was performed as a double-blind, randomized, crossover trial. Each subject was tested in four different test sessions at 1-wk intervals. Subjects received intravenous injections of either 0.1 mg/kg of midazolam or saline (rate of injection, 30 s); 4 h later the subjects consumed a beverage that either did or did not contain 0.7 g/kg of alcohol. The dose of midazolam used was a high normal dose usually given during ambulatory procedures (surgical or medical) in this age group. The dose of alcohol used was approximately equivalent to 1.4 L of beer, 950 mL of wine, or 180 mL of hard liquor and would be expected to result in a blood alcohol level of approximately 0.6 mg/100 mL (13.0 mmol/L) in a fasting 70-kg male. The lemonade-and-lime flavored beverages that contained alcohol had 10% ethyl alcohol by volume in the 450 mL (per 70 kg) that subjects

consumed in 20 min. Beverages were served cold in cups.

Before the first session of the experiment, subjects were trained (three practice sessions) to use the apparatus in order to prevent further learning of the task during the actual testing. Psychomotor tasks and subjective effects evaluations (see below) were performed before intravenous sedation and 1, 3, 5, and 7 h after intravenous sedation. Blood alcohol levels were measured before intravenous sedation and 5 and 7 h after intravenous sedation (1 and 3 h after beverage consumption). A snack was served approximately 2 h after drug injection, and lunch was served to subjects approximately 6 h after drug injection (1.5 h after alcohol ingestion).

Psychomotor effects, mood, and blood alcohol levels served as the dependent measures in this study. The Maddox wing test was used to measure esophoria and exophoria and motor function of the eyes (8). An action judgment tester, similar to a driving test, was used to measure eye-hand coordination; using a steering wheel, subjects attempted to keep two pointers on a moving track without striking objects; number of mistakes (i.e., when pointers struck objects) was recorded. Body sway was measured by using a computerized strain gauge technique to reveal defects in vestibular, motor, and proprioceptive functions; subjects stood on a force plate for 60 s with their eyes closed, and variations in movement of the anterior-posterior and lateral direction were recorded. Subjects performed three psychomotor tests on a computer (Apple Macintosh). Simple auditory and visual reaction times were determined by measuring the time it took the subject to press a button after hearing a sound or seeing a letter on the computer screen. Eye-hand coordination was measured by having the subject track a moving circle on a computer screen with a cross controlled by a "mouse." Coordination mistakes were measured by counting the number of times that the cross exceeded a certain distance from the target circle. Coordination accuracy was obtained by measuring the mean distance (in pixels) between the cross and the circle during the test.

Subjective effects were measured at baseline and 1, 3, 5, and 7 h after drug injection with the Profile of Mood States (POMS). The POMS, chosen because it is sensitive to transient mood states, consists of 72 adjectives commonly used to describe transient mood states (9). Subjects indicate how they feel at the moment in relation to each of these adjectives, from "not at all" (0) to "extremely" (4). Eight clusters of items have been previously derived using factor analysis and have been given names that best de-

scribe the clustered adjectives (anxiety, depression, anger, vigor, fatigue, confusion, friendliness, and elation).

Blood alcohol level was measured from breath air using an Alco-sensor 3 breath analyzer (Intoximetrics Instruments, St. Louis, Mo.).

For each test, repeated-measures multivariate analysis of variance (10) was used to study the effect of drug (present or absent) and of alcohol (present or absent), and the interaction of these effects if any. P < 0.05 was considered significant. Post hoc tests were used, when significant drug or alcohol effects were obtained, to determine the duration of psychomotor performance impairment. In addition, we determined whether significant learning effects were present by using week of testing as a covariate.

Results

Table 1 presents psychomotor performance and subjective effects measures before and 1 and 3 h after intravenous injection of either saline (averaged across the two saline conditions, i.e., saline injectionplacebo beverage and saline injection-alcohol beverage) or midazolam (averaged across the two midazolam conditions, i.e., midazolam injection-placebo beverage and midazolam injection-alcohol beverage). Midazolam caused significant impairment in auditory and visual reaction times, eye-hand coordination, action judgment, and esophoria/exophoria (all P < 0.001 except eye-hand coordination accuracy for which P < 0.01). Elation (P < 0.05), friendliness (P < 0.05) 0.01), and vigor (P < 0.001) scores from the POMS significantly decreased after midazolam, whereas confusion (P < 0.001), depression (P < 0.05), and fatigue (P < 0.001) scores significantly increased. In general, effects of midazolam peaked at 1 h after injection and had dissipated by 3 h after injection. The two exceptions were esophoria/exophoria and fatigue scores; these dependent measures were still significantly elevated 3 h after injection.

Mean \pm sp blood alcohol concentration 1 h after alcohol ingestion was 0.56 ± 0.13 mg/100 mL (12.2 \pm 2.8 mmol/L). In most states, a motorist with a blood alcohol concentration of 1 mg/100 mL (21.7 mmol/L) is considered to be driving under the influence of alcohol. Table 2 presents psychomotor performance and subjective effects measures at baseline (0 h) and 1 and 3 h after ingestion of either the placebo beverage (averaged across the two placebo conditions, i.e., saline injection-placebo beverage) or the alcohol beverage (averaged across the two alcohol conditions, i.e.,

placebo injection-alcohol beverage and midazolam injection-alcohol beverage). Alcohol caused significant impairment in eye-hand coordination (accuracy, P < 0.005; mistakes, P < 0.01), action judgment (P < 0.001), and esophoria/exophoria (P < 0.005); these impairing effects had dissipated by 3 h after ingestion. Confusion scores (POMS) increased (P < 0.005) after alcohol administration and remained significantly elevated 3 h after beverage ingestion. Subjects were also more fatigued and friendly (P < 0.05).

In no instance was any significant interaction noted between residual midazolam and alcohol. The analyses of covariance using weeks as a covariate revealed that no significant learning effects took place during the study.

Discussion

The number of freestanding ambulatory surgery centers grew from 39 in 1982 to nearly 1000 in 1988 and it is estimated that by 1990 about 40% of all surgical procedures performed in the United States will be done in surgicenters (11,12). It is difficult to know exactly, but at least 60%–75% of these procedures probably involve either general anesthesia or intravenous sedation. Patients are routinely released after ambulatory surgery or endoscopy when they have demonstrated rudimentary psychomotor functioning (e.g., ability to get dressed and to walk without assistance). However, this does not mean that the whole spectrum of psychomotor functioning (including those skills necessary to safely operate a motor vehicle, cook, or care for small children) has returned to normal. Many of the drugs used in ambulatory surgery for analgesia or sedation are known to impair various psychomotor functions well after the patient is released from the surgicenter or endoscopy suite (13). If patients drink alcohol and then drive, cook, or even care for children, they may be increasing the risk of harm to themselves or others because of alcohol/drug interactions.

In the present study, midazolam and alcohol independently impaired psychomotor performance and affected mood. The impairment of performance by midazolam is consistent with a number of other studies that have documented the deleterious effects of benzodiazepines on psychomotor/cognitive performance (2,3,14). The impairment for the most part was not long-lasting; most measures of psychomotor performance had returned to baseline levels by 3 h after the injection. The alterations in mood by midazolam in the present study, including increases in sedation and confusion, have been noted in other studies

<u>Table 1</u>. Measurements of Psychomotor Performance and Mood at Baseline (0 h) and 1 and 3 h After Either Saline or Midazolam Injections^a

	Saline injection		Midazolam injection				
	0 h	1 h	3 h	0 h	1 h	3 h	P
Auditory RT (ms)	0.270	0.263	0.257	0.253	0.373	0.260	0.001
, , ,	± 0.011	± 0.009	± 0.008	± 0.01	± 0.035 ^b	± 0.01	
Visual RT (ms)	0.355	0.322	0.318	0.344	0.433	0.333	0.001
	± 0.015	± 0.011	± 0.009	± 0.013	$\pm 0.033^{b}$	$\pm \ Q.011$	
Eye-hand coordination	17.0	15.8	16.8	16.8	31.5	20.6	0.001
(mistakes)	± 2	± 1.6	± 1.8	± 2.3	$\pm \ 3.5^{b}$	± 2.1	
Eye-hand coordination	11.4	11.2	11.6	11.8	19.4	13.4	0.01
(MDFC)	± 0.4	± 0.4	± 0.5	± 0.5	$\pm 2.1^{b}$	± 0.9	
Action judgment	27.6	23.9	24.2	30.0	57.9	31.0	0.001
(mistakes)	± 4.5	± 4.2	± 4.5	± 5.1	$\pm 6.3^{b}$	± 4.7	
Esophoria/exophoria	3.1	3.6	3.4	3.2	7.0	4.7	0.001
(diopters)	± 0.6	± 0.6	± 0.6	± 0.6	± 0. <i>7</i> ⁶	$\pm~0.6^{c}$	
Body sway—	627.9	774.8	744.2	7 08.1	1963.7	908.5	NS
anterior-posterior (pixels)	± 37.6	± 39.8	± 48.8	± 50.8	± 519.4	± 84.7	
Body sway—lateral (pixels)	648.8	805.9	733.7	811.1	1819.2	884.6	NS
	± 39.5	± 61.3	± 48.1	± 99.5	± 476.6	± 81.3	
POMS anxiety (score)	0.1	0.0	-0.0	0.2	0.0	-0.1	NS
• • • • • • • • • • • • • • • • • • • •	± 0.1	± 0.1	± 0.0	± 0.1	± 0.0	± 0.0	
POMS depression (score)	0.2	0.1	0.1	0.3	0.2	0.1	0.05
• , , ,	± 0.1	± 0.0	± 0.0	± 0.1	± 0.0	± 0.0	
POMS anger (score)	0.3	0.2	0.2	0.3	0.2	0.2	NS
	± 0.1	± 0.0	± 0.1	± 0.0	± 0.0	± 0.0	
POMS vigor (score)	1.4	1.4	1.3	1.3	1.0	1.1	0.001
	± 0.1	± 0.1	± 0.1	± 0.1	$\pm 0.1^d$	± 0.1	
POMS fatigue (score)	0.8	0.6	0.6	0.8	1.2	0.9	0.001
	± 0.1	± 0.1	± 0.1	± 0.1	$\pm 1.2^{b}$	± 0.1°	
POMS confusion (score)	0.1	0.0	0.0	0.1	0.4	0.1	0.001
• •	± 0.1	± 0.1	± 0.1	± 0.1	$\pm 0.1^{b}$	± 0.1	
POMS friendliness (score)	1.8	1.9	1.8	1.8	1.5	1.6	0.01
	± 0.1	± 0.1	± 0.1	± 0.1	$\pm 0.1^d$	± 0.1	
POMS elation (score)	1.1	1.1	1.1	1.2	1.3	1.1	0.05
	± 0.1	± 0.1	± 0.1	± 0.1	± 0.1	± 0.1	

MDFC, mean distance from center of circle, measured in pixels; NS, main effect not significant; RT, reaction time.

Values are mean ± se.

examining the effects of benzodiazepines on mood (15,16).

Alcohol had an impairing effect on psychomotor performance, but to a lesser extent than that of midazolam. The dose of alcohol that was used in the present study was roughly equivalent to 1.4 L of beer, 950 mL of wine, or 180 mL of hard liquor. Other studies assessing the impairing effects of alcohol using amounts similar to the one we used have reported mixed results. Some studies find substantial psychomotor impairment (2,17), whereas other studies find only mild (18,19) or no impairment (4,20,21). It is probable that had a higher dose of alcohol been used in the present study, psychomotor impairment

would have been more severe, but we wanted to use a dose of alcohol that was relevant to our clinical situation.

No major interaction was noted between residual midazolam and alcohol. These results stand in contrast to a number of other studies that have documented that benzodiazepines potentiate the effects of alcohol (2,4–7,14). However, differences in results between the present study and these other studies can probably be accounted for by differences in interval between drug administration: in the other studies benzodiazepines and alcohol were jointly administered, whereas in the present study, the interval between the two was set at 4 h. The half-lives

^{*}Significance (P value) is based on repeated measures multivariate analysis of variance comparing midazolam with saline, using hours 0, 1, 3, 5, and 7 as time points.

Difference score (1 h - 0 h) in midazolam injection condition significantly different (P < 0.001) from difference score (1 h - 0 h) in saline injection condition. Difference score (3 h - 0 h) in midazolam injection condition significantly different (P < 0.0025) from difference score (3 h - 0 h) in saline injection condition.

Difference score (1 h - 0 h) in midazolam injection condition significantly different (P < 0.01) from difference score (1 h - 0 h) in saline injection condition. Difference score (3 h - 0 h) in midazolam injection condition.

<u>Table 2</u>. Psychomotor Performance and Mood Measures at Baseline (0 h) and 1 and 3 h After Either Placebo or Alcohol Beverage (and 5 and 7 h After Either Saline or Midazolam Injections)^a

	Placebo beverage			Alcohol beverage			
	0 h	5 h	7 h	0 h	5 h	7 h	P
Auditory RT (s)	0.263	0.272	0.250	0.260	0.292	0.256	NS
, ,,	± 0.011	± 0.008	± 0.008	± 0.01	± 0.011	± 0.01	
Visual RT (s)	0.353	0.323	0.314	0.347	0.346	0.311	NS
、 ,	± 0.014	± 0.009	± 0.01	± 0.015	± 0.011	± 0.01	
Eye-hand coordination	17.1	17.8	15.5	16.7	24.4	18.2	0.01
(mistakes)	± 2.2	± 1.8	± 1.7	± 2.2	$\pm 2.5^{b}$	± 2.2	
Eye-hand coordination	11.8	11.7	11.7	11.4	12.7	11.8	0.005
(MDFC)	± 0.6	± 0.5	± 0.5	± 0.4	$\pm 0.6^{c}$	± 0.5	
Action judgment	28.8	26.1	26.0	28.7	32.5	27.3	0.001
(mistakes)	± 4.8	± 3.9	± 4.3	± 4.8	$\pm 4.9^{d}$	± 4.2	
Esophoria/exophoria	2.9	3.3	3.2	3.3	5.2	4.0	0.005
(diopters)	± 0.6	± 0.6	± 0.6	± 0.7	± 0.7°	± 0.6	
Body sway	651.9	716.5	740.7	684.1	950.2	778.1	NS
anterior-posterior (pixels)	± 36.8	± 55.8	± 68.7	± 52.2	± 117.1	± 85.6	
Body sway—lateral (pixels)	671.1	719.3	721.4	788.8	868.7	743.8	NS
,	± 45.5	± 51.5	± 49.2	± 97.9	± 89.7	± 67.6	
POMS anxiety (score)	0.2	0.0	0.0	0.1	-0.1	-0.0	NS
, , ,	± 0.1	± 0.1	± 0.0	± 0.1	± 0.1	± 0.0	
POMS depression (score)	0.3	0.2	0.1	0.2	0.1	0.1	NS
	± 0.1	± 0.1	± 0.0	± 0.06	± 0.0	± 0.0	
POMS anger (score)	0.3	0.3	0.3	0.3	0.2	0.2	NS
	± 0.1	± 0.1	± 0.1	± 0.0	± 0.1	± 0.0	
POMS vigor (score)	1.3	1.4	1.5	1.4	1.4	1.2	NS
	± 0.1	± 0.1	± 0.1	± 0.1	± 0.1	± 0.1	
POMS fatigue (score)	0.9	0.6	0.6	0.7	0.7	0.9	0.05
	± 0.1	± 0.1	± 0.1	± 0.1	± 0.1	$\pm 0.1^f$	
POMS confusion (score)	0.1	0.1	0.0	0.1	0.4	0.2	0.005
- · ·	± 0.1	± 0.1	± 0.1	± 0.1	$\pm 0.1^{b}$	$\pm 0.1^f$	
POMS friendliness (score)	1.8	1.7	1.6	1.8	1.9	1.6	0.05
• •	± 0.1	± 0.1	± 0.1	± 0.1	± 0.1	± 0.1	
POMS elation (score)	1.2	1.2	1.1	1.1	0.9	1.0	NS
	± 0.1	± 0.1	± 0.1	± 0.1	± 0.1	± 0.1	

MDFC, mean distance from center of circle, measured in pixels; NS, main effect not significant; RT, reaction time.

of midazolam and triazolam are similar (22,23). Recently, an interaction between triazolam and alcohol was noted: three neurologists were described who used triazolam to reduce jet lag, drank alcohol (albeit not at a level to be intoxicated), and then developed anterograde amnesia (24). The time frame between triazolam and alcohol ingestion was probably similar to that of our study. However, no impairment of activity was described. Other factors may have contributed to the amnesia: two of the three were taking other long-term medications and their sleep was disrupted by the long air ride. It appears, then, that the residual effects of the short-acting benzodiazepine, midazolam, do not potentiate to any great degree the effects of alcohol given 4 h or more later.

It should be acknowledged that the generality of these results may be somewhat limited by the lack of parametric manipulations of midazolam and alcohol doses, and interdrug interval, as well as the use of only young, healthy men. It is possible, for example, that had an interdrug interval shorter than 4 h been used, more significant midazolam-alcohol interactions may have been obtained. However, such results would be less meaningful to anesthesiologists and other medical personnel because patients typically would arrive home no sooner than 3–4 h after ambulatory surgery. No midazolam or alcohol doseresponse analyses were performed because we wanted to use clinically relevant doses of both drugs. Similarly, we did not include either women or older

[&]quot;Significance (P value) is based on repeated measures multivariate analysis of variance comparing alcohol with placebo, using hours 0, 5, and 7 as time points.

Difference score (5 h - 0 h) in alcohol beverage condition significantly different (P < 0.005) from difference score (5 h - 0 h) in placebo beverage condition. Difference score (5 h - 0 h) in alcohol beverage condition significantly different (P < 0.01) from difference score (5 h - 0 h) in placebo beverage condition. Difference score (5 h - 0 h) in alcohol beverage condition significantly different (P < 0.025) from difference score (5 h - 0 h) in placebo beverage condition. Difference score (5 h - 0 h) in alcohol beverage condition significantly different (P < 0.001) from difference score (5 h - 0 h) in placebo beverage condition.

Difference score (7 h - 0 h) in alcohol beverage condition significantly different (P < 0.01) from difference score (7 h - 0 h) in placebo beverage condition.

patients. It is clear that alcohol pharmacokinetics may differ as a function of gender, although it is not so clear whether psychomotor, cognitive, or subjective responses to alcohol are affected by gender (25-28). Similarly, midazolam elimination half-life is prolonged significantly and total clearance is decreased significantly in elderly as opposed to younger subjects or patients (29,30). We are presently conducting additional studies to see if longer acting drugs commonly used in ambulatory surgical procedures will interact with alcohol when drug injection precedes alcohol ingestion by several hours. In these studies, we will also be including women and older subjects to examine the role of menstrual cycle and age. However, the results of the present study suggest that if patients are sedated only with midazolam during ambulatory surgery, then any deleterious effects of midazolam on psychomotor performance will have probably dissipated by the time the patient arrives home, and that effects from alcohol ingested at home will probably not be influenced by the recent administration of midazolam.

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Review Article

Anesthetic Implications of the Renin-Angiotensin System and Angiotensin-Converting Enzyme Inhibitors

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Key Words: HORMONES, RENIN-ANGIOTENSIN. POLYPEPTIDES, RENIN-ANGIOTENSIN. ENZYMES, ANGIOTENSIN-CONVERTING. PHARMACOLOGY, INHIBITORS OF ANGIOTENSIN-CONVERTING ENZYME.

Hemodynamic stability and control of sympathetic stimulation are important goals in critically ill patients whether in the perioperative or nonoperative states. Much has been written concerning the potential benefits of blockade of cardiovascular responses during the perioperative period, including blunting of the elevation of plasma levels of well-known "stress" hormones (1–5). Although the renin-angiotensin system (RAS) is but one arm in the array of the so-called "stress response" during surgery, aspects of the role it normally plays both in nonsurgical and in abnormal, pathological states continue to be elucidated (6-9). As such, the role of angiotensin-converting enzyme (ACE) inhibitors in clinical practice, as well as the number of such medications available and being investigated, also continues to become clearer (10-13). The role that the RAS itself plays during surgery and anesthesia has not only led to a better understanding of cardiovascular and renal physiology in those contexts, but has also initiated examination of the usefulness of RAS interruption during stressful operations (14-16).

Because of the recent accumulation of a large amount of new data on this subject, this review is designed to define and update the mechanisms and implications of RAS activation, as well as the mechanisms and goals of RAS blockade, both in and outside of the operating room. In this way we hope to put into perspective how the RAS fits into the scheme of hemodynamic responses perioperatively and the potential manipulations we have at our disposal for the control of these responses.

The Renin-Angiotensin System in Normal Physiology

The role of the RAS as an important regulator of cardiovascular physiology in humans has been well established (17). Along with the sympathetic nervous system, renal function, sodium-retaining and sodiumlosing hormones, and dietary sodium intake, the RAS is involved in control of blood pressure, particularly under stress conditions. The system is initiated as the acid protease renin, synthesized from its precursor prorenin, is secreted by the juxtaglomerular cells of the kidney in response to a variety of stimuli (Figure 1). These stimuli include decreases in blood pressure in the renal artery, decreases in sodium delivery to the macula densa (and/or possibly that of chloride [18]), and sympathetic nervous system activation. Accordingly, at least in the normotensive state, high sodium levels and sympathetic nervous system inhibition tend to blunt renin release. Renin, in turn, cleaves its substrate, angiotensinogen, a hepatically synthesized α_2 -globulin, to generate the decapeptide angiotensin I. Neither peptide is thought to be biologically active, although angiotensin I is rapidly converted to the octapeptide angiotensin II by ACE or kininase Π (19). The pulmonary circulation appears to be the major site of ACE activity, although ACE is also found in the vascular endothelium of the heart,

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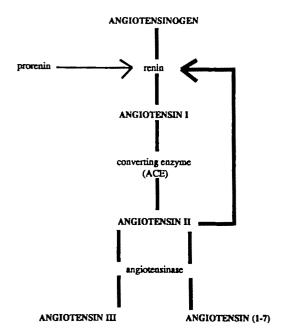


Figure 1. The renin-angiotensin homeostatic loop.

kidney, adrenal cortex, testes, and brain, as well as in the lung (20).

Angiotensin II is a well-known potent vasopressor and also stimulates aldosterone secretion by the adrenal cortex. In addition to a variety of local, endorgan effects to be discussed, angiotensin II also has an inhibitory effect on the vagus and causes peripheral facilitation and ganglionic stimulation of the sympathetic nervous system (21–23). The peptide partially suppresses renin secretion by a direct effect on the juxtaglomerular cells, thus completing its own homeostatic regulatory loop (19,24). Finally, angiotensin II is degraded in the plasma to the C-terminal heptapeptide angiotensin III or the N-terminal heptapeptide angiotensin (1-7), both of which are thought to be biologically active (25,26). It can be seen, then, that with decreases in blood pressure or sodium delivery to the macula densa, or with sympathetic stimulation (all of which occur after hemorrhage, dehydration, or surgery), RAS activation eventually leads to angiotensin II formation. This results in a restoration (or increase) in blood pressure as well as sodium retention caused by enhanced secretion of aldosterone. Together, the increased perfusion pressure, salt retention, and angiotensin II levels lead to suppression of further renin release unless the initiating stimulus continues unabated.

It should be emphasized that despite our familiarity with this intricate endocrine system, the global RAS does not have an obligatory role in blood pressure maintenance in the normal, sodium-replete,

intact individual (19). Hall et al. have substantiated that it is primarily the feedback of sodium and water excretion on arterial pressure, often referred to as the renal-pressure natriuresis mechanism, that mainly affects long-term blood pressure control (27–29). In short, hydrostatic forces act to increase or decrease sodium and water excretion in order to maintain a stable glomerular filling pressure. This, in turn, affects venous return, cardiac output, and eventually systemic blood pressure. Superimposed on this basic mechanism, under stress conditions, are various neurohumoral control systems that include the sympathetic nervous system, the antidiuretic hormone (ADH), atrial natriuretic hormone (ANH), and prostaglandins as well as the RAS. Importantly, some of these control systems augment the action of the RAS, whereas others counteract its effects.

For instance, it is well known that β -adrenergic agonists initiate renin release, whereas β -adrenergic antagonists and centrally acting α_2 -agonists inhibit it. In addition, not only does ADH enhance the effect of the RAS by vasoconstriction and increased reabsorption of water in the collecting ducts of the nephron, but ADH release is triggered by stimuli that may also trigger the RAS-namely, hypotension, decreased central blood volume, stress, anesthetics, and surgical stimulation (30,31). These stimuli may activate ADH despite the fact that plasma osmolality appears to be its primary regulator (32). Conversely, ANH and some prostaglandins oppose the activity of the RAS and act to "regulate" its actions. Atrial natriuretic hormone is stored in and released from human atrial myocytes in response to increased vascular volume, increased atrial pressure, epinephrine, and ADH (33). The primary effects of ANH include direct peripheral vasodilation, suppression of ADH release, and inhibition of aldosterone secretion, as well as increased glomerular filtration, natriuresis, and diuresis (34).

Finally, some prostaglandins, in particular prostaglandin E₂, are thought to counteract the renal vaso-constrictive properties of angiotensin II in stressful or pathological conditions in an attempt to maintain renal blood flow (35). Angiotensins appear to be powerful stimuli to prostaglandin secretion in the kidney. Indeed, Terragno et al. found that indomethacin decreases renal blood flow significantly in anesthetized and laparotomized dogs (36). In addition, an abundance of literature exists concerning the possible deleterious effects that prostaglandin inhibition may have on renal function in patients with RAS activation, including those with congestive heart failure (CHF), systemic lupus erythematosis, cirrhosis, Bartter's syndrome, and premature infants undergoing

<u>Table 1</u>. Tissue Renin-Angiotensin Systems and Their Functions

Tissue	Proposed functions of RAS
Blood vessels	Increases peripheral vascular tone; directly stimulates vascular hypertrophy
Myocardium	Constricts coronary vessels; augments contractility; exacerbates reperfusion injuries
Kidney	Increases glomerular hydraulic pressure; aids in sodium reabsorption
Brain	Increases adrenergic outflow; elicits thirst; generates vasopressin/catecholamine release
Adrenal gland	Stimulates aldosterone secretion
Placenta	Decreases blood flow in preeclampsia
Jejunum	Generates electrolyte and water reabsorption
Uterus	Renin production initiates preeclamptic symptoms
Ovary	Regulates ovulation and hormone production
Testes	Regulates hormone production
Pituitary gland	Regulates prolactin release

RAS, renin-angiotensin system.

closure of a patent ductus arteriosis (37–40). Apparently, prostaglandin inhibition allows unopposed, severe, angiotensin II constriction to reduce significantly the renal blood flow and glomerular filtration rate (GFR) in these patients.

As with other physiologic systems, activation or inhibition of the RAS, then, is accompanied by a host of simultaneous actions and reactions from other neurohumoral systems, all of which affect the RAS. It should also be appreciated that chemical disruption of the RAS may not only affect elements of that system but other integrated systems as well.

Probably the most important recent advance in the understanding of the function of the RAS centers on the evolving concept of local, end-organ, reninangiotensin systems (41). The existence of such systems has partially explained the effectiveness of renin inhibitors, angiotensin antagonists, and ACE inhibitors in controlling hypertension that is associated with normal or suppressed plasma renin activity (42,43). To date, components of the system have been found not only in the kidney but also in adrenal cortex, endothelial and smooth muscle cells of blood vessels, myocardium, central nervous system, and placenta, as well as salivary gland, jejunum, uterus, ovary, testes, and pituitary gland (18,41,44–48) (Table 1).

The possible functions of some of these local RASs are extensive. For example, in blood vessels, local vascular RASs may participate in the regulation of

regional vascular tone and blood flow in such a way that abnormal activation of these local systems may be implicated in the pathogenesis of chronic hypertension and the development of vascular hypertrophy (41). In myocardium, the possible roles of local angiotensins include those of coronary vasoconstrictors, endogenous inotropes, or stimulators of myocardial hypertrophy, although by far most research has centered on the effect the RAS has during ischemia or reperfusion injuries. Indeed, the concept that angiotensin may further reduce blood flow or increase oxygen consumption during postischemic reperfusion was investigated by Linz et al., who demonstrated that reperfusion arrhythmias in the rat heart were aggravated by perfusion with either angiotensin I or II (49). Furthermore, these authors also found that angiotensin-enhanced ventricular fibrillation was completely eliminated by the ACE inhibitor ramipril, accompanied by improved cardiac hemodynamics including maximum dP/dT, myocardial oxygen consumption, and coronary blood flow. Others have shown that, experimentally, captopril may limit myocardial infarction size by increasing coronary blood flow (50). In the future, it is possible that inhibitors of the RAS may have a place as "stabilizers" in the periischemic period.

Renal effects of angiotensin II appear to include not only feedback inhibition on renin production and stimulation of aldosterone secretion, but also efferent arteriole vasoconstriction and increased proximal tubular sodium reabsorption as well (51,52). This selective constrictive action on efferent arterioles helps prevent reduction in glomerular hydrostatic pressure and GFR in various pathophysiologic conditions such as those associated with decreased renal perfusion, chronic sodium deprivation, or fixed obstructions proximal to the renal cortex (53). These renal effects are probably more a result of the actions of intrarenal RASs than of the circulating system. Finally, recent evidence indicates that angiotensinogen and renin mRNA are both expressed in the brain (54,55). This, along with the fact that the blood-brain barrier is relatively impervious to the actions of circulating angiotensin II (56), provides strong support for the existence of an endogenous brain RAS. Brain angiotensins may contribute to the regulation of blood pressure, thirst, and vasopressin as well as catecholamine release (22,23).

Other tissue RASs are listed in Table 1. It is clear from the above discussion that local RASs may be just as important as the circulating RAS in providing cardiovascular and neurohumoral homeostasis, if not more so. In fact, some analogies can be drawn between the RAS and the sympathetic nervous system

in that tonic control of local vascular function is provided by local noradrenergic nerve activity, and while under stress, additional support is provided by the release of catecholamines from the endocrine adrenal medulla (41). The same may apply for the RAS, especially as more evidence accumulates regarding these local system functions.

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Blockade of the Renin-Angiotensin System/ Angiotensin-Converting Enzyme Inhibitors

The aspect of the RAS that most clinicians are familiar with is probably responses to inhibition of the system itself. Although the RAS may be antagonized at several levels along its cascade (including by renin inhibitory proteins, monoclonal antibodies to renin, and angiotensin II antagonists), by far the most clinically useful of the inhibitors of the RAS have been the ACE inhibitors. The first ACE inhibitor, teprotide, was a peptide recovered from the venom of the South American snake, Bothrops jararaca. This peptide was found to inhibit circulating kininase activity and thus prevent the degradation of bradykinin (57,58). As it was later found that this kininase also enzymatically converted angiotensin I to angiotensin II (ACE), teprotide not only became the first clinically used ACE inhibitor but also helped to disclose considerable information about the action of ACE as well as about the complexities of the RAS. Teprotide's inactivation by oral administration greatly limited its clinical use, however.

The three commonly used ACE inhibitors at present include captopril (Capoten, Squibb), enalapril (Vasotec, Merck), and, most recently, lisinopril (Prinivil, Merck or Zestril, Stuart) (Table 2). All three are available for oral administration, although enalaprilat (Vasotec, Merck), the in vivo active metabolite (diacid) of enalapril, was recently introduced for clinical use as an intravenous preparation (59,60). This intravenous ACE inhibitor may prove to be useful in the perioperative period. Other ACE inhibitors currently under investigation are included in Table 2, and at least five additional compounds have been quoted in the literature as of this writing (61).

Converting enzyme inhibitors can be classified according to the structural element that interacts with the zinc ion of the enzyme as well as the form in which the agent is administered—"prodrug" (parent, inactive form) or active compound. Captopril and alacepril bind to the enzyme by means of a sulfhydryl group; the others, including enalapril and lisinopril, do not. Significantly, the sulfhydryl group was implicated as a cause of the high incidence of adverse side

<u>Table 2</u>. Pharmacologic Effects of Single Doses of Converting-Enzyme Inhibitors in Hypertensive Patients

			- L	
Agent/dose	Prodrug (inactive)	Time of onset (min)	Time of peak effect (h)	Duration of effect (h)
Captopril (100 mg)	No	1530	1–2	610
Enalapril (20 mg)	Yes	60–120	4-8	18–30
Lisinopril (10 mg)	No	60	2–4	18–30
Pentopril (750 mg)	Yes	30	2–3	10–18
Ramipril (20 mg)	Yes	30–60	3–8	24–60
Alacepril (50 mg)	Yes	30	2–3	6–10

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effects in early trials of captopril (62), although eventually most undesirable effects were found to be related to the administration of excessively high doses (63). The "prodrugs" were developed to increase the rate of absorption and/or to prolong the action of the active agent. This is exemplified when comparing the onset of action and time to peak effect of the active drug captopril to the "prodrug" enalapril (Table 2).

The major difference, however, among clinically used ACE inhibitors is in duration of their actions. The short elimination half-life of captopril (2 h) appears to be due in part to its oxidation to the dimer and mixed sulfides, all of which are eventually excreted renally (64). Conversely, the long elimination half-life and thus duration of effect of enalapril and lisinopril reflect the strong binding of the drugs to serum ACE (61). As with captopril and its metabolites, the kidney is also the primary route of elimination for enalaprilat and lisinopril, and thus elimination is retarded in the presence of renal insufficiency. In patients with impaired renal function, reduction in dosage or lengthening of intervals between dosing is necessary with all currently used ACE inhibitors.

The pharmacology of ACE inhibitors is relatively simple, but their mechanisms of action are more complex than might be inferred. By blocking the conversion of angiotensin I to angiotensin II, ACE inhibitors prevent angiotensin II-mediated vasoconstriction and angiotensin II-stimulated activation of the sympathetic nervous system. Aldosterone con-

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centrations tend to decrease after dosaging, although the effect is usually transient (65). In addition, a marked increase in plasma renin activity is observed in healthy volunteers as well as in patients with hypertension, reflecting inhibition of the negative feedback effect that angiotensin II has on renin secretion (66,67).

In the short term at least, and especially in states of a highly active RAS (sodium depletion, dehydration), the above progression explains most of the expected hemodynamic effects of converting enzyme inhibition. Interestingly, however, several lines of research indicate that inhibition of plasma ACE does not fully explain the spectrum of longer term effects of ACE inhibitors (10). For instance, ACE inhibitors are effective in forms of hypertension not associated with the activation of the RAS. Accordingly, there is no consistent relationship between inhibition of the RAS and the antihypertensive effects of these drugs as shown by the fact that the duration of hypotensive effects seen with ACE inhibitors exceeds the duration of ACE inhibition in plasma (68,69). This has led to the concept that inhibition of tissue ACE, not plasma ACE, is more likely to be the mechanism of the pharmacodynamic effects of ACE inhibitors. Support for this is provided in the observation that the decrease in blood pressure seen with converting enzyme inhibitors correlates better with the degree of inhibition of the tissue RAS than with the circulating levels of components of the RAS (45). The poor correlation between the clinical effects of ACE inhibition and plasma levels of ACE and angiotensin has also led to the speculation that it is the increased levels of bradykinin and, in turn, prostaglandins (PGE₂), both vasodilators, that in part accounts for the hypotensive effects of the drugs (70). This follows because ACE degrades bradykinin as well as angiotensin I, and bradykinin is thought to stimulate the production of several prostaglandins. Evidence to support this theory, however, remains conflicting at the present time (61,70).

The clinical effects of ACE inhibitors appear to be consistent within subgroups of patients. In normal or hypertensive subjects without heart failure, all converting enzyme inhibitors reduce blood pressure by lowering total peripheral resistance with little change in heart rate, cardiac output, or pulmonary wedge pressure (71–73). In the presence of CHF, the reduction in afterload results in a substantial improvement in cardiac output and stroke volume with increases of 15%–40% at peak effect (61). The absence of reflex tachycardia with ACE-inhibitor administration, unlike the increase in heart rate seen with other drugs that decrease afterload, has yet to be adequately

explained, although enhancement of parasympathetic activity (or disinhibition) (74) and a druginduced venodilatory action have been suggested (70).

The renal hemodynamic effects of ACE inhibitors vary according to sodium balance, hydration, and the presence or absence of hypertension and/or renal artery stenosis. For example, in the sodium-replete, normovolemic subject in whom the RAS is not appreciably activated, renal blood flow and GFR do not vary in response to RAS interruption (75). This is in contrast to the marked increase in renal blood flow and GFR seen in hypertensive patients after ACE inhibition, especially in the presence of concomitant intravascular dehydration and sodium depletion associated with diuretic therapy (76,77). Conversely, patients with renal artery stenosis, especially bilateral stenosis, may suffer a dramatic decrease in GFR and renal function as a result of ACE-inhibitor therapy (78,79). This is attributed to blunting of angiotensin II-mediated efferent arteriolar constriction necessary to maintain glomerular capillary perfusion in patients with renal artery stenosis (80).

Finally, converting enzyme inhibition may have important consequences in the function of the sympathetic nervous system. Although studies in humans have not found consistent changes in circulating catecholamine levels after drug administration (81), a reduced responsiveness of arterioles to pressor agents has been demonstrated in both normal and hypertensive subjects after ACE inhibition (82,83). This most likely reflects blockade of the previously mentioned interactions between angiotensin II and the sympathetic nervous system, and may have obvious implications for the critically ill patient requiring exogenous catecholamines in the perioperative period.

The anesthesiologist should be aware that the primary reasons for the increase in popularity of ACE inhibitors relate to their proven efficacy and scant profile of common side effects. In fact, patients comply much better with therapy with converting enzyme inhibitors than with any other class of antihypertensives (71). Angiotensin-converting enzyme inhibitors are free of many of the central nervous system side effects that are associated with conventional agents, including depression, sleep disturbances, fatigue, and sexual dysfunction. Other adverse effects, such as heart failure, bronchospasm, bradycardia, and exacerbation of peripheral vascular disease, that are seen with β -blockers are not seen with ACE inhibitors. Similarly, metabolic changes such as hypokalemia, hyponatremia, hyperglycemia, hyperuricemia, and hyperlipidemia induced by di1991:72:667-83

Table 3. Frequency of Adverse Effects of Captopril and Enalapril

	Captopril (%)	Enalapril (%)
Cough	0.5	1.3
Rash	4.0	1.3
Taste disturbance	2.0	1.4
Angioedema	0.1	0.2
Proteinuria (>1 g/day) ^a	0.7	0.7
Neutropenia (<1000 white cells on two occasions)	< 0.05	?

The side effects shown (except proteinuria) occurred with frequencies higher than those with placebo in patients who received comparable doses and had no renal insufficiency.

"Frequency in control group, 0.5%.

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uretic therapy are not observed with either captopril or enalapril. Moreover, captopril and enalapril reduce the hypokalemia associated with hydrochlorothiazide when given together and may even increase serum potassium levels slightly in some patients (84).

Adverse reactions to ACE inhibitors may be classified as those that are inherent in their mechanisms of action and those that are not. As discussed above, deteriorating renal function may be seen in patients with renal artery stenosis. Likewise, hyperkalemia has been observed with institution of ACE-inhibitor therapy in patients with marginal renal function, in part due to loss of aldosterone-mediated potassium secretion. Probably the most common side effect seen with initiation of therapy, however, is hypotension. Patients at risk include those whose blood pressure is dependent on RAS activation due to severe dehydration, sodium depletion, renovascular hypertension, or severe CHF. Often dose reductions or discontinuation of ACE-inhibitor therapy is required in these patients.

Adverse side effects of captopril and enalapril not related to their mechanisms of action are listed in Table 3. Although the more benign signs and symptoms, including rashes and taste disturbances, are the most common side effects and seldom require withdrawal of therapy, significant angioedema or neutropenia, although rare, may be life-threatening and may warrant immediate discontinuation of this class of drug (70,71).

Angiotensin-Converting Enzyme Inhibition in Disease States

Although hypertension and CHF are at present the only approved indications for ACE inhibitors, the list

Table 4. Medical Indications for Use of Angiotensin-Converting Enzyme Inhibitors

- A. Clinical indications (approved)
- 1. Hypertension
- 2. Congestive heart failure
- B. Clinical indications (not approved at present)
 - 1. Renovascular hypertension
 - 2. Scleroderma renal crisis
 - 3. Idiopathic edema
 - 4. Reduction of proteinuria
 - 5. Protection against diabetic glomerulopathy
 - 6. Bartter's syndrome
 - Raynaud's phenomenon (primary)
 - 8. Takayasu's disease
- C. Experimental indications
 - 1. "Cardioprotection"
 - 2. Hepatorenal syndrome
- 3. Subarachnoid hemorrhage

of proposed uses is extensive (Table 4). Probably the most surprising of proposed uses is the use of converting enzyme inhibitors in "renal protection," despite the preceding discussion emphasizing the opposite. It is imperative that anesthesiologists understand the physiology behind ACE-inhibitor therapy in various disease states, and, possibly more important, that they realize that such therapy is designed for use in the chronic, maladaptive state. In fact, ACE inhibition in many acute disease states may only serve to blunt neurohumoral mechanisms designed to preserve vital organ perfusion.

Hypertension

The pathogenesis of hypertension in humans is multifactorial and beyond the scope of this discussion. We know, however, that the RAS, the sympathetic nervous system, ADH, sodium and water retention, and vessel wall properties interact to generate both acute and chronic abnormally high blood pressures. Nonetheless, the efficacy of all three ACE inhibitors has been proven in hypertension associated with high and normal or low levels of plasma renin (85-87). Again, this probably reflects inhibition of the RAS with decreased angiotensin II effects in the circulation and, more important, in the tissues. Converting enzyme inhibitors are as effective as any other class of antihypertensives when used as monotherapy (70), and it is this reason, as well as the lack of side effects, that has brought ACE inhibitors popularity as first-line drugs, as opposed to their previous third- or fourth-line positions. It should also be noted that the rebound hypertension seen with clonidine has not been observed with ACE inhibitors.

The treatment of certain subgroups of hypertensive patients has recently aroused much interest in the use of converting enzyme inhibitors. Patients with renovascular hypertension due to renal artery stenosis respond well to ACE-inhibitor therapy, as would be expected given their high plasma renin activity (88,89). Such medical therapy can be used either as a screening test for renovascular hypertension or for control of blood pressure in patients with unilateral renal artery stenosis and a normal contralateral kidney. For reasons stated previously, converting enzyme inhibitors are usually reserved either as adjuncts to surgery or angioplasty in patients with bilateral renal artery stenosis or, rarely, as medical therapy for those same patients who may pose high surgical risks.

It is well established that hypertensive crises associated with many collagen vascular diseases and, in particular, with scleroderma are renin-mediated. Accordingly, ACE inhibitors currently are considered to be the agents of choice in patients with these disorders (90). Unfortunately, this group of patients also has the highest rate of side effects with these drugs.

Hypertension of pregnancy may in part result from release of uterine renin and stimulation of angiotensin II production with the subsequent appearance of hypertension, sodium retention, and a reduced GFR (91). Although the short-term use of ACE inhibitors during human pregnancy in preeclampsia has been reported (92,93), no controlled trials have yet been published. More important, because administration of these drugs to pregnant animals has been associated with decreased neonatal survival and increased fetal wastage, use of ACE inhibitors in pregnant women is not recommended at present (11).

Probably most promising is the increasing use of ACE inhibitors in the prevention of deterioration of renal function in patients with chronic renal insufficiency. It is postulated that the progressive decline in renal function in diabetics, particularly those with hypertension, is the result of increased intraglomerular pressures augmented by inappropriate angiotensin II-mediated efferent arteriole constriction (94). With chronic reductions of glomerular pressures, with or without systemic blood pressure control, the administration of captopril (and presumably other ACE inhibitors) to diabetic patients with proteinuria or other evidence of renal dysfunction may reduce the rate of deterioration of function (95–97). Longer term studies are presently underway comparing ACE inhibitors with other antihypertensive agents in this

Finally, the value of converting enzyme inhibitors for the treatment of perioperative hypertension remains problematic. With the advent of intravenous enalaprilat, patients chronically treated with ACE inhibitors who are unable to tolerate oral medication can continue with their antihypertensive therapy without interruption. The recommended dosage for enalaprilat is 1.25 mg intravenously every 6 h. Caution must be advised, as with other antihypertensives, for its initial or continued use in those perioperative, hypertensive patients whose RAS is activated in response to hemodynamic derangements including blood loss, dehydration, pain, and renal artery thrombosis. Obviously, therapy in these clinical situations needs to be directed to the primary disorder because RAS interruption may not only serve to mask further clinical signs, but may precipitate hemodynamic compromise as well-e.g., hypotension and acute renal failure. There is evidence to suggest that captopril pretreatment in animals effectively inhibits the recovery of blood pressure and renal perfusion after acute hypovolemic hypotension induced by moderate hemorrhage (98,99). Enalaprilat may be particularly worrisome in this context given its long duration of action (Table 2). Thus, administration of ACE inhibitors perioperatively must be done with considerable knowledge of a patient's blood volume and electrolyte status as well as use of other drugs or factors that may influence the activation of the RAS.

Congestive Heart Failure

The efficacy of disruption of the RAS in the treatment of CHF can be understood with a knowledge of the neurohumoral changes seen in this disease (Figure 2). In acute CHF, a series of compensatory changes take place in an attempt to maintain cardiac output and vital organ perfusion. These include catecholaminemediated increases in heart rate and venoconstriction, the latter of which increases ventricular filling thus allowing utilization of the Frank-Starling mechanism to improve myocardial contractility. Together, sympathetic stimulation and reduced renal perfusion cause release of renin by the juxtaglomerular cells of the kidney and therefore activation of the RAS. In this setting, angiotensin II serves not only to maintain a systemic and glomerular perfusion pressure by vasoconstriction, but also assists in increasing sodium retention, intravascular volume, and thus myocardial filling pressures by stimulation of aldosterone secretion. Clearly, interference with any of these acute changes, including ACE inhibition, may only lead to further hypoperfusion.

On the other hand, in the chronic state, these initial compensatory changes become ineffective in

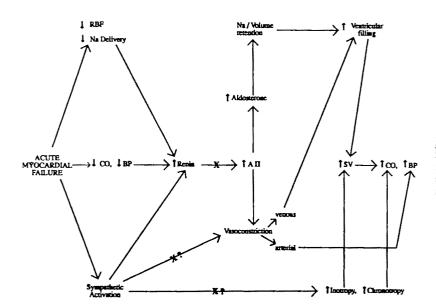


Figure 2. Compensatory neurohumoral responses in acute congestive heart failure. "X" denotes interference by ACE inhibitors. CO, cardiac output; BP, systemic blood pressure; RBF, renal blood flow; Na, sodium; A II, angiotensin II; SV, stroke volume.

improving hemodynamics and, in fact, may contribute to detrimental volume retention and vasoconstriction. Because the failing heart often functions on the flat portion of the Frank–Starling curves (100), improvements in contractility through preload reserves are exhausted, with the result that the heart may become exquisitely sensitive to changes in afterload (101). These pathophysiological considerations have led to the use of drugs that reduce afterload in the treatment of chronic CHF, among which ACE inhibitors appear to be the most widely accepted (102).

All three clinically available converting enzyme inhibitors have been shown to cause significant hemodynamic improvements in patients with chronic CHF including decreases in systemic vascular resistance and increases in cardiac index (102-105). Heart rate may be unchanged or slightly decreased (104,106). Right atrial pressure and pulmonary arterial and pulmonary capillary wedge pressures fall as well (102). These responses apparently occur in patients with both high and low plasma renin activity, suggesting that mechanisms other than inhibition of plasma ACE, including effects on tissue ACE, sympathetic withdrawal, and/or increases in bradykinin/ prostaglandins, may account for the hemodynamic changes that are seen (107). It is noteworthy that controlled trials have consistently shown improvements in symptomatology, duration of treadmill exercises, left ventricular ejection fraction, and New York Heart Association classification when currently used ACE inhibitors were compared with placebo (105,106,108,109). Probably most pertinent is the finding that ACE-inhibitor therapy has been shown to lower the expected mortality in patients with severe heart failure (110). The CONSENSUS Trial study group recently reported that the addition of enalapril to conventional therapy in patients with advanced CHF reduced mortality by 27% (111). These results apparently were independent of the fact that ACE inhibitors exert antiarrhythmic effects of their own.

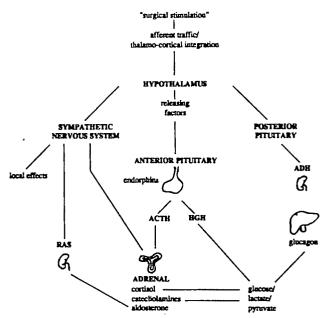
It is clear that the favorable results accruing from the use of converting enzyme inhibitors will mean a more widespread use of the drugs. From a perioperative viewpoint, the anesthesiologist must then know the possible anesthetic implications from ACEinhibitor therapy and the possible uses of these medications intraoperatively. Central to such a discussion, however, are the concepts regarding responses of the RAS to surgery and anesthesia.

Responses of the Renin-Angiotensin System to Surgery and Anesthesia

The activation of the RAS during anesthesia and surgery is only one part of the endocrine and metabolic response that is seen (Figure 3). Included among these "stress" hormones are also catecholamines, ADH, cortisol, endorphins, glucagon, and human growth hormone, as well as glucose, lactate, and pyruvate (112). Although it is not clear whether total abolition of these responses is desirable (113), increases in such hormones can cause arrhythmias, unwanted cardiovascular stimulation, decreases in renal blood flow, retention of salt and water, and catabolism (114,115). From the previous discussions, it is evident that activation of the RAS and other

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<u>Figure 3</u>. The neuroendocrine response to surgery. ACTH, adrenocorticotropic hormone; HGH, human growth hormone; ADH, antidiuretic hormone.

hormones for that matter, represents an adaptive response that may, unfortunately, accelerate into a potential maladaptive state. The response to surgical stimulation may fall into this category. It would be useful, then, to examine those commonly encountered hemodynamic scenarios in which the RAS plays a role either as a deleterious actor or as a physiologic reactor in order to determine the appropriateness of treatment possibilities.

It is generally accepted that surgery itself is a potent initiator of the RAS (116). Increases in plasma renin activity accompany elevations of other wellknown "stress" hormones. Most evidence, however, seems to point to the fact that anesthetics, independent of surgical stimulation, cause little if any increase in renin activity. Little change in plasma renin activity has been reported in rats, for example, during induction and maintenance of 1 MAC anesthesia with inhalation agents or intravenous ketamine (117). Similar findings were reported in surgical patients given inhalation or spinal anesthetics for a variety of operations (118). These findings, of course, must be viewed in light of a subject's blood volume status and hemodynamic response to anesthetics. For instance, similar studies also find higher baseline plasma renin activity and higher rises in renin with induction of anesthesia in the presence of sodium (119) or volume depletion (118). That the RAS, in addition, plays a significant role in the maintenance of blood pressure during anesthesia has also been verified by the observation that significant decreases in mean systemic pressures occur in rats given saralasin, an angiotensin II antagonist, after establishment of halothane or enflurane but not ketamine anesthesia (117). The same has recently been confirmed in humans given halothane or isoflurane anesthesia (120).

One way of viewing the above findings is that any activation of the RAS associated with anesthetic induction (but not tracheal intubation) most likely represents a physiologic response to dehydration or hypotension associated with subsequent sympathetic stimulation and renin release. This can be contrasted with the significant increases in plasma renin activity often seen with surgical stimulation as part of the exaggerated hormonal response to surgery. The question of interruption of the RAS in both regards is discussed below.

Probably the hemodynamic scenario most closely associated with integration of the RAS involves patients undergoing controlled hypotension, particularly with sodium nitroprusside (SNP). Renin activity as well as catecholamine levels more than double during induced hypotension in humans with SNP (121), perhaps as an attempt of the hormone system to limit the hypotensive actions of the vasodilator. There is also a direct relationship between SNP dosage used to induce hypotension in rats and plasma renin activity, with or without anesthesia (122). Both these studies (121,122) concluded that activation of the RAS with controlled hypotension using SNP may be responsible for the so-called "resistance" to the hypotensive actions of the drug, as well as for the often-seen rebound hypertension after cessation of SNP. This adaptive RAS response may, in fact, become maladaptive because controlled hypotension is often a desirable hemodynamic state for many procedures.

Another perioperative situation involving the RAS is hypertension after cardiac surgery with cardiopulmonary bypass (CPB). Because the RAS may be activated by CPB, several investigators have implicated angiotensin II as being responsible for the vasoconstriction and potentially dangerous hypertension often seen after cardiac procedures (15,16,123-125). Such hypertension may increase the incidence of bleeding, cerebrovascular accidents, and/or myocardial ischemia in these patients. The subject remains somewhat controversial because data must be interpreted in light of different anesthetic techniques, duration and temperature of CPB, and types of oxygenators used, as well as the concomitant administration of exogenous catecholamines or vasodilators. These factors may all, in fact, influence hormonal levels. On the other hand, most evidence indicates that whether extracorporeal circulation is pulsatile or nonpulsatile does not influence plasma renin activity during CPB (126–128).

In an early study in which moderate doses of morphine anesthesia, bubble oxygenators, and moderate hypothermia (32°C) were used in patients undergoing coronary artery bypass grafting (CABG), a good correlation was found between plasma renin activity and increases in intraoperative mean arterial blood pressure (123). Renin levels also increased during bypass as well as postoperatively in patients, although not necessarily in association with hypertension. In a larger study, increases in plasma renin activity postoperatively were greater in hypertensive than in normotensive patients, although the differences were not significant (124). Angiotensin II levels have likewise been shown to increase markedly during CPB and to persist for 4-24 h postoperatively (15,125), although its causal relationship to postoperative hypertension has yet to be conclusively proven in well-controlled trials. Nevertheless, the hypothesis that residual angiotensin II levels post-CPB lead to disturbing vasoconstriction and hypertension has opened the way for examination of the usefulness of RAS inhibitors in that context.

Finally, the subject that has sparked the most interest in studies of the RAS intraoperatively has to be the pathophysiological changes involving suprarenal or infrarenal aortic cross-clamping. The characteristics of the systemic hemodynamic consequences due to aortic cross-clamping in patients undergoing aortic surgery are well documented (129–131). The mechanisms underlying the development of acute renal failure after aortic surgery are, however, less well studied, despite an associated mortality rate of more than 30% (132). The role that stimulation of the RAS has in reducing intraoperative renal blood flow and producing postoperative renal failure has been described in both thoracic and abdominal aortic procedures.

A few laboratory studies have shown that thoracic aortic occlusion with or without a mechanical means of maintaining distal aortic perfusion results in elevation of plasma renin activity correlating with reductions in renal blood flow (133–136). Interestingly, these changes persist in dogs for up to 30 min after both 30 min or 1 h of thoracic aortic occlusion (137,138). Infrarenal aortic cross-clamping, at least in humans, is associated with up to a 38% decrease in renal blood flow (139). The correlations with increases in renin levels are indirect but substantiated. Infrarenal aortic cross-clamping in dogs, for example, produces significant increases in renin activity that may be responsible for the corticomedullary redistribution of intrarenal blood flow that is seen (140). In

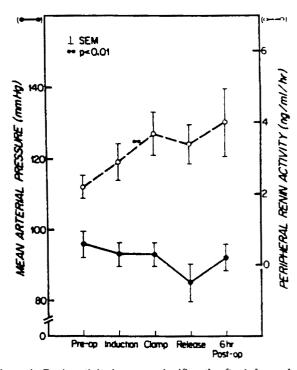


Figure 4. Renin activity increases significantly after infrarenal aortic cross-clamping and remains elevated 6 h postoperatively. Postoperative renin activity is higher than the preoperative level (P < 0.01). Note that corresponding changes are not observed in mean arterial pressure. SEM, standard error of the mean. (Reproduced with permission from Grindlinger GA, Vegas AM, Williams GH, Mannick JA, Hechtman HB. Independence of renin production and hypertension in abdominal aortic aneurysmectomy. Am J Surg 1981;141:472–7.)

patients undergoing abdominal aortic surgery, renin activity increases and peaks after unclamping of the aorta with the elevation persisting well into the postoperative period (141,142) (Figure 4). The question of whether the changes in renin levels are the cause or the result of decreases in renal blood flow postoperatively is unclear and difficult to resolve because those stimuli that diminish renal blood flow during aortic clamping also stimulate renin release (e.g., surgery, sympathetic stimulation, emboli). As with post-CPB hypertension, the possibility that activation of the RAS is the culprit behind postoperative hypertension and, more important, deteriorations in renal function allows investigation into the usefulness of ACE inhibitors in aortic surgery as well.

Uses of Angiotensin-Converting Enzyme Inhibitors During Surgery and Anesthesia

By far the most common use of ACE inhibitors in the perioperative period comes as part of a patient's oral antihypertensive regimen. As with other antihypertensive agents, the current consensus regarding ACE-inhibitor therapy perioperatively is to continue all such drugs up until surgery and to restart therapy as soon as possible postoperatively. Although most clinicians agree with this, there is concern regarding potential hemodynamic instability with perioperative administration of ACE inhibitors. Recently, impressive, prolonged hypotension has been reported in patients undergoing general anesthesia for minor surgery in whom ACE inhibitors were given before surgery (143). In addition, decreased cerebral blood flow (corrected for Paco₂) associated with hypotension after anesthetic induction has been reported in healthy patients given preoperative captopril but not metoprolol or placebo (144). Although in this no attempt was made to correlate findings with intraoperative cerebral function (electroencephalogram) or postoperative neurologic deficits, discontinuing ACE-inhibitor treatment preoperatively was recommended.

It is doubtful that such findings will have an impact on established anesthetic practice. Certain conditions or surgical procedures do, however, warrant special attention from the anesthesiologist when considering perioperative ACE-inhibitor administration. Surgical procedures involving significant blood or "third space" losses often require the release of catecholamines and other "stress" hormones to maintain vital organ perfusion. Also, the RAS may play a key role in blood pressure maintenance during inhalational anesthesia (117,120). Angiotensinconverting enzyme inhibition, because of its ability to eliminate angiotensin II-mediated sympathetic stimulation, may reduce arteriole responsiveness to endogenous and exogenous pressors and thus impair the actions of catecholamines (82,83). Moreover, recovery of blood pressure and renal perfusion after hypotensive hemorrhage is significantly impaired in the presence of ACE inhibition (98,99). These problems may be compounded with the use of the longer acting agents, enalapril and lisinopril, whose effect on serum or tissue ACE may last anywhere from 18 to 48 h (70). Thus, it does not seem unreasonable to consider discontinuation of long-acting ACE inhibitors preoperatively in patients scheduled or emergently about to undergo extensive surgical procedure involving large blood or fluid shifts. A variety of shorter acting intravenous antihypertensive agents may be more suitable in such clinical circumstances, should such therapy become necessary.

Captopril (and presumably other ACE inhibitors) reduces the dose requirement for SNP during induced hypotension (121,145). This follows logically given the above discussion of the activation of the

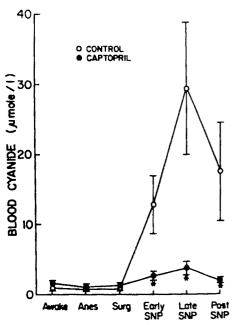


Figure 5. Whole blood cyanide before, during, and after SNP infusion used for induced hypotension in patients undergoing spinal fusion. All values are expressed as mean \pm SEM. *P < 0.05, captopril versus control. (Reproduced with permission from Woodside J, Garner L, Bedford RF, et al. Captopril reduces the dose requirement for sodium nitroprusside induced hypotension. Anesthesiology 1984;60:413–7.)

<u>Table 5</u>. Uses of ACE Inhibitors Perioperatively

Reference	Authors	Types of patients/ surgery	Drug used
14	Kataja et al.	HTN/CAD/AAA	Captopril
146	Cashman et al.	CAD/CABG	Captopril
147	Yates & Hunter	Healthy/GYN	Enalapril
148	McCarthy et al.	Healthy/GYN	Captopril
149	Murphy et al.	Healthy/GYN	Enalaprilat
150	Niarchos et al.	CAD/CABG	Captopril
151	Colson et al.	CAD/CABG	Captopril
152	Roberts et al.	CAD/CABG	Not stated
153	Colson et al.	CAD/CABG	Captopril

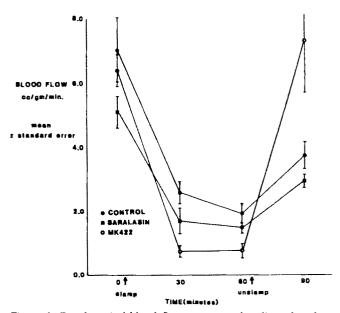
HTN, hypertension; CAD, coronary artery disease; AAA, abdominal aortic aneurysm; CABG, coronary artery bypass grafting; GYN, gynecologic surgery.

RAS during SNP-induced hypotension. Not only is the dose of SNP needed to produce hypotension decreased after 3 mg/kg captopril in patients undergoing spinal fusion, but blood cyanide levels are significantly less in treated patients as well (145) (Figure 5). In addition, rebound hemodynamic changes, including increases in catecholamines or aldosterone, are not seen in captopril-pretreated patients after cessation of SNP-induced hypotension (121).

The intentional use of ACE inhibitors before or during anesthesia and surgery to gain improved systemic or renal hemodynamic control has received little attention in the literature. Table 5 lists the major evidence examining ACE-inhibitor use in the perioperative period in humans.

As discussed previously, the RAS takes part in the cardiovascular response to surgical stimulation and, probably, to tracheal intubation. Unfortunately, unlike studies evaluating the use of β -blockers, narcotics, local anesthestics, or nitrates, a paucity of information exists regarding the ability of preoperative ACE inhibitors to blunt hemodynamic responses to intubation or incision. This is not surprising given the relatively long onset and duration of action of ACE inhibitors compared to commonly used shorter acting intravenous antihypertensive drugs. Nonetheless, studies on this subject are disappointing. For instance, oral captopril has been said not to affect the hemodynamic response to sternotomy in patients undergoing CABG receiving moderate doses of narcotics (146). When 5 mg oral enalapril is given to patients 4 h before induction of anesthesia, mean arterial pressure, but not heart rate, is lower after intubation and incision than when placebo injections are given (147). Sublingual captopril administered immediately before induction of anesthesia in healthy patients has similar effects on blood pressure, although it is associated with significant increases in heart rate after intubation and impressive bouts of hypotension during surgery (148). Similarly, intravenous enalaprilat given to patients before induction of anesthesia in doses sufficient to completely inhibit plasma ACE, is not able to prevent significant increases in mean arterial pressure or heart rate associated with tracheal intubation as compared with patients receiving saline (149). From this data it is doubtful, given the pharmacokinetics of ACE inhibitors together with the risk of delayed hypotension sometimes seen with their use, that these agents can be considered to be practical when used to alleviate exaggerated cardiovascular responses during induction of anesthesia or stimulation from surgery.

The majority of the studies listed in Table 5 involve ACE inhibitors used in patients undergoing CABG, with specific attention focused on the effects on postoperative hypertension. As it is believed by some that hypertension after CABG is a result of RAS activation (15,124,125,150), the use of converting-enzyme inhibitors makes sense. Although preoperative captopril does not seem to affect the incidence of postoperative hypertension after CABG (151), two reports indicate that intravenous converting-enzyme inhibitors given postoperatively can control hypertension as effectively as SNP without untoward tachycardia (150,152). As expected, systemic vascular



<u>Figure 6</u>. Renal cortical blood flows return to baseline after thoracic aortic clamp release in MK 422-treated (intravenous enalaprilat) dogs and are significantly higher than in dogs given saralasin or placebo (P < 0.016). Of note, saralasin infusions were not continued after release of the clamp, which may explain the findings. (Reproduced with permission from Joob AW, Harman K, Kaiser DL, Kron IL. The effect of renin-angiotensin system blockade on visceral blood flow during and after thoracic aortic cross-clamping. J Thorac Cardiovasc Surg 1986;91:411–8.)

resistance can be reduced as much as 50% while cardiac output increases concomitantly. Likewise, we have observed similar hemodynamics using intravenous enalaprilat after cardiac surgery in hypertensive patients whose volume status is stable (unpublished data).

Interestingly, comparisons of hemodynamics and renal function in patients undergoing CABG given either preoperative captopril or placebo and undergoing hypothermic nonpulsatile bypass reveal that renal plasma flow, GFR, and urinary sodium excretion are better in patients given the ACE inhibitor as compared with control patients (153). Although no patients developed postoperative renal failure in either group of this study, it is possible that this renal "protective" effect may be useful in patients at risk for renal dysfunction after CPB. Further studies are needed to confirm this interesting finding.

Finally, despite some evidence examining how the RAS acts in the hemodynamic and renal consequences of aortic cross-clamping, little has been published regarding the effect that RAS interruption has in this context. Renal cortical blood flow was significantly better 30 min after thoracic aortic unclamping in dogs given intravenous enalaprilat during clamping than in control dogs (138) (Figure 6). This occurred despite a similar cardiovascular hemodynamic

status in the two groups, which may point to the benefits of disrupting the RAS after removal of an aortic clamp to avoid the "rebound" decreases in renal blood flow possibly mediated by the RAS (137-139,141,142). Studies in humans are, unfortunately, difficult to undertake. In a recent prospective, randomized trial of patients undergoing infrarenal aortic surgery, however, hemodynamic data, during and after aortic cross-clamping as well as postoperatively, did not significantly differ between patients given 25-mg doses of oral captopril before induction of anesthesia and control patients given nothing (14). Significantly, more episodes of hypotension requiring volume resuscitation before cross-clamping were reported in the treated group. Interestingly, however, urine output in the captopril group was almost twice that of the control group during anesthesia and remained higher for the first 24 h postoperatively despite similar hemodynamic profiles between groups. It is plausible, but not proven, that the ACE inhibitor may have been responsible for the improved urine flow, although no further determinants of renal function were made. In contrast, at our institution a similar trial is presently in progress substituting intravenous enalaprilat administered before crossclamping instead of oral captopril given before induction of anesthesia. Preliminary results are encouraging, such that postoperative creatinine clearance and GFR (as assessed by DTPA-technetium 99 clearance) appear to be greater in patients in the treated group than in those of the control group (unpublished data).

In summary, it is clear that the lack of data concerning the use of ACE inhibitors in surgery and anesthesia hinders valid conclusions of its perioperative use. Most convincing are the data on use of captopril pretreatment before SNP-induced hypotension. Conversely, it is difficult to recommend use of oral or intravenous drugs to produce ACE inhibition for blunting of cardiovascular responses to tracheal intubation or incision, especially in light of an abundance of evidence showing that shorter acting intravenous agents are effective for that purpose. The most exciting areas involve the potential use of ACE inhibitors in conditions in which the RAS may be the culprit behind detrimental systemic or renal hemodynamic changes, e.g., aortic cross-clamping and hypertension after CPB. Hopefully, more experience with ACE inhibitors, combined with an increasing number of experimental and clinical trials involving these drugs, will reveal more information on the appropriateness of administration of ACE inhibitors in association with anesthesia and surgery.

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Historical Article

Among the First: The Career of John Henry Evans, MD

Douglas R. Bacon, MD, and Clifton K. Yearley, PhD

BACON DR, YEARLEY CK. Among the first: the career of John Henry Evans, MD. Anesth Analg 1991;72:684-92.

During his 46-year career, John Henry Evans, MD, significantly guided anesthesia's evolution from a field dominated by lay practitioners toward one in which the preeminent role was played by physicians. Widely recognized as an expert on supplemental oxygen therapy as well as the developer of subcutaneous oxygen as an adjuvant treatment for several chronic diseases, Evans throughout his years of practice held an academic appointment at the University of Buffalo.

From that post he tirelessly employed professional political persuasion, combined with a high order of organizational skill, to help create and expand the importance of residencytrained anesthesiologists. As president of the Associated Anesthetists of the United States and Canada, complemented by a quarter-century tour on the International Anesthesia Research Society's Board of Governors, he significantly contributed to the development of anesthesiology into its current form.

Key Words: HISTORY, JOHN H. EVANS.

The preeminence of physician specialists in anesthesia was largely a 20th-century phenomenon in the United States. One of the seminal figures in this first era of anesthesiologists—if not the leading figure of his generation—was John Henry Evans, MD (Figure 1). Trained at the University of Buffalo School of Medicine, he was to spend his entire career within 50 miles of its clinical campus. Inspired by the legendary surgeon Roswell Park and having settled comfortably to a university system familiar to him, Evans accepted his initial academic appointment as instructor in anesthetics in June 1913. During his subsequent career, he would preside over the university's establishment of a Department of Anesthesia, variously serving as its first professor, first chairman, and finally as its first professor emeritus.

As a consequence of his efforts on behalf of fledgling professional anesthesia societies in the early decades of this century, Evans progressively rose to national and then international prominence. In July

1927, the British Journal of Anaesthesia generously dedicated an entire issue to reviewing his achievements; in that same year Evans presided over the Associated Anesthetists of the United States and Canada, the only national anesthesia organization of the time. As president of the Board of Governors of the International Anesthesia Research Society, he helped guide the only international group of anesthesiologists and oversaw publication of the specialty's sole U.S. publication, Current Researches in Anesthesia and Analgesia, until journalistic competition arrived in 1940. Moreover, in the course of 33 years, 29 of his articles appeared in the leading medical journals of his time, a consequence of his exhaustive investigations into all aspects of anesthesia: inhalation gases, psychology, the physiologic change affected by anesthesia, and the teaching of the specialty. Such accomplishments notwithstanding, Evans remained an enigma even within the locus of his work in Buffalo, New York, and, regrettably, his own profession has substantially forgotten his contributions.

Evans' origins were unprepossessing. He was born to Welsh immigrant parents on September 24, 1876, in the predominantly Welsh village of Freedom, New York. He learned English only after his family moved in 1886 to Machias, New York, where his father ran the general store (Figure 2), supporting Evans, his two brothers, and three sisters. Formal

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<u>Figure 1</u>. John Henry Evans, MD. (Photograph courtesy of the Wood Library-Museum.)

education came in the Ten Broek Academy in nearby Franklinville and in Ithaca High School (1), with no indications of any predisposition toward a medical career.

Indeed, his path to medicine was circuitous. Because eye trouble closed many occupations to him, he spent nearly 6 years in the Merchant Marine, traveling principally to ports in South America, Cuba, the Caribbean, and eventually to other parts of the world (2). Having finally resettled in western New York, he enrolled in the University of Buffalo School of Medicine, from which he graduated in 1908 with honors, at the then advanced age of 32 (Figure 3) (3). After four additional years as a house physician at the Buffalo General Hospital (4), he established what became a successful general practice (Figure 4) in Machais and courted his future wife in nearby Franklinville. It was the tragic death of his brother in a train accident that led to his return to Buffalo (5).

Welcomed back to his indigenous medical community, Evans was soon a respected colleague of Buffalo's leading surgeons, most notable among them the already internationally renowned Roswell Park. Repeating experiences of his days as a house officer, he began administering anesthetics, all the while nourishing the anomalous idea of specializing in anesthesia (6), just as the University of Buffalo was investigating an effective way to instruct medical students in this "new" field of medicine. The need



<u>Figure 2</u>. Evans Family General Store, Machias, N.Y. (Photograph courtesy of the Evans family.)

for such training, in fact, had been recognized by the university as early as 1909 (7), and, with the caution characteristic of academia, a definitive decision was not hammered out by its executive faculty until June 2, 1913. At Roswell Park's insistence, the university created the position of assistant in anesthetics, a post for which Park had essentially groomed Evans and which Evans, when offered, swiftly accepted (8).

Evans' academic responsibilities required the teaching of medical students, for which he was compensated at two dollars per student taught, instructing an average of 40 students a term (9). Estimates of his teaching abilities differ. One of his former medical students recalled that he was so preoccupied with private practice that he rarely came to his classes (10), an observation partially confirmed by a fellow anesthesiologist who described Evans as a "technician—only interested in private practice" (11). At the beck and call of Buffalo's most prominent surgeons, Evans needed as many private cases as possible to secure financial stability for his family. Compensation for the physician anesthetist averaged five dollars a case (12), about one-tenth that of the surgeon; when coupled with an "enormous financial



<u>Figure 3</u>. University of Buffalo School of Medicine classes of 1907–1911. John Henry Evans, second row first person on the left. (Photograph courtesy of the Evans family.)



Figure 4. Office of John Henry Evans, MD, Machias, N.Y. (Photograph courtesy of the Evans family.)

loss in the stock market crash of 1929" (13), private practice became a necessary priority over teaching.

Despite these difficult circumstances, however, Evans was concerned with imparting his knowledge to succeeding generations of physicians. Another former medical student characterized him as a pleasant, if not popular, professor, who "met with six to eight students two or three times," discussing the monitoring of anesthetized patients, various anesthetic agents, and how to ascertain the patient's level of anesthesia. None of these sessions involved patient contact (14).

Of Evans' teaching curriculum nothing remains. Depictions of his instruction therefore must be in-

ferred from his writing. Evans' world of anesthetics was divided into two broad categories: "the revocable" and the "irrevocable." Ease of control characterized revocable anesthetics, affording swift elimination in instances of overdosing. These, of course, included inhalation anesthetics: ether, nitrous oxide, ethylene, chloroform, and ethyl chloride. Near irreversibility distinguished the irrevocable agents, which consisted of the various local anesthetics, cocaine, Stovaine, Neocaine, Novocaine (procaine), quinine urea hydrochloride, and the intravenous agents sodium amytal and Pernocton, as well as rectal Avertin and ether. Evans believed the routine use of irrevocable agents to be unjustified, and pre-

ferred inhalation of nitrous oxide (with or without ether), citing statistical substantiation of this preference (15) and expressing his concern over the paralysis that occasionally accompanied spinal anesthetics (16).

Evans firmly espoused the close monitoring of patients: careful charting of blood pressure and pulse rates in major cases and on poor risk patients was essential (17). Similarly, he believed proper preoperative examination and assessment to be imperative, in order that patients be "in the best possible condition" to meet the demands of surgery (18). Indeed, an encapsulation of his philosophy of anesthetics exists in his summation of objectives in cases of children undergoing tonsillectomies:

- 1. A pleasant induction.
- 2. Maintenance of a quiet throat during the operation with preservation of the cough reflex.
- 3. Assistance to the surgeon in the operation.
- 4. Prevention of inspiration of foreign matter into the lungs.
- 5. Availability of equipment for resuscitation and familiarity with the various steps necessary for its application (19).

More important, Evans believed in visiting his patients postoperatively, often administering supplemental oxygen therapy (20).

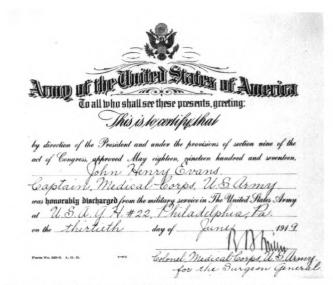
Apparently, the university was well satisfied with Evans' performance. On May 15, 1917, the chairman of Surgery, Dr. James J. Gibson, successfully urged the executive faculty to pass Evans' promotion to instructor in anesthetics (21). The following year the Medical School, in its bulletin, advertised "Special Instruction in Anesthesia" as a fourth-year medical student elective under Evans' supervision (22).

Early in 1918 the student welfare committee complained that no "definitive schedule [had been] laid out for the assignment of students for instruction in anesthetics" (23). Resolution of this crisis must have been delayed, for shortly thereafter, Evans was commissioned a captain in the United States Army Medical Corps (Figure 5). Leaving behind an infant son Alfred and toddler daughter Ann, he served until he was honorably discharged on June 13, 1919 (Figure 6) and compensated for a severe sinus infection contracted during his military service (24).

After his return to civilian life, the university ceased to pay Evans to teach the medical students but continued to support his academic profile as volunteer faculty. In 1924, the chairman of Surgery again successfully recommended Evans for promotion before the Medical School's executive faculty. He be-



<u>Figure 5</u>. Medical Corps Commission. (Courtesy of the Evans family.)



<u>Figure 6</u>. Discharge from the U.S. Army Medical Corps. (Courtesy of the Evans family.)

came an associate in anesthetics (25). But in 1925 a controversy arose around Evans, one perhaps behind which he was at least an initiating force: the University of Buffalo School of Medicine clinical faculty sought changes in policies and practices within both the university and the large, charity-based Buffalo City Hospital. An affiliate of the University of Buffalo

School of Medicine, Buffalo City Hospital was one of several hospitals used as clinical campus for the instruction of medical students. It was in a position to become the primary teaching hospital in Buffalo during the 1920s; politics prevented the designation (26), even to the present day.

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The initial provocation for change came from that tireless, wheelchair-bound, arthritic physician anesthetist, Francis Hoeffer McMechan, who is now famed for helping organize anesthesiologists throughout the United States and Canada and for fighting tenaciously for professional recognition of anesthesiology, both in university medical schools and hospitals—not the least because progress in surgery compelled it. McMechan, then secretary of the Associated Anesthetists of the United States and Canada and a close personal friend of Evans, had written a letter outlining a substantial proposal (unfortunately now lost) concerning the teaching of anesthesia, which the Buffalo City Hospitals' administrative board felt possessed merit; but no changes could be effected without the approval of the hospitals' board of managers (27). Evans' involvement certainly stemmed from the fact that he and Mc-Mechan were old political allies; both had assumed active roles in early organizational efforts in anesthesia and enjoyed mutual respect.

Certainly not coincidentally, 2 months later, in May 1925, the University of Buffalo's executive faculty of the School of Medicine gathered to consider another letter, this one from Dr. N. P. Colwell, secretary of the American Medical Association's (AMA) Council on Medical Education and Hospitals. Colwell's letter, in fact, had been inspired by Mc-Mechan's complaint to him and the AMA about anesthesia instruction for medical students and interns at the primary teaching hospitals in Buffalo— The Buffalo General, The Buffalo City, The Children's and The Sisters of Charity Hospitals—and was most likely based on data supplied by Evans. The Buffalo Medical School's executive faculty empowered an investigative committee of several of Buffalo's leading physicians: Drs. McGuire, Wende, and Trick (28). McGuire and Trick were both surgeons for whom Evans regularly administered anesthesia, and he had acknowledged 9 years earlier that he was deeply indebted—among other reasons—for their having provided him with cases requiring nitrous oxideoxygen anesthesia (29).

Against that background, Evans was asked to submit to the McGuire, Wende, and Trick investigative triumvirate a written report covering his teaching activities during 1925. Because rapid action is not a hallmark of academia, the committee completed its charge 6 months later, yielding three basic results. Interns, first of all, were not receiving proper instruction in anesthesia because the attending anesthetist had insufficient time—between teaching, using ward cases, and pursuing private work—to provide it. Second, because of the chronic shortage of physician anesthetists, surgeons, reportedly "against their will," were constrained to hire nurse anesthetists. But the third finding was more positive: the committee noted that all undergraduate students were receiving adequate instruction in anesthesia (30).

Anesthesia thereafter did not trouble the Buffalo Medical School's executive faculty until March 16, 1932, when two additional physicians were granted voluntary posts: Dr. Oscar Stover as an associate in anesthesia, and Dr. Clarence J. Durshordwe, Evans' partner, as an assistant in anesthesia (31). Less than a month later, Evans received his appointment as a professor of anesthesia (32). By 1936, Evans' publications identified a Department of Anesthesia (33); 2 years later the *University of Buffalo Bulletin* cited him as professor and head of the Department of Anesthesia (34)—full recognition that an academic department had finally materialized.

Growth characterized the 9 years Evans presided over his fledgling department. Although, curiously, the records of the executive faculty of the University of Buffalo Medical School indicate an appointment of a hospital assistant (the equivalent of a modern resident) in anesthesia and surgery at the Buffalo City Hospital in 1932 (35), it was not until 1937 that the board of managers of the Buffalo City Hospital contemplated creating its own Department of Anesthesia (36). No other hospital assistants in the field were appointed by the Buffalo Medical School until Dr. Rose Lenahan, a University of Buffalo graduate, arrived at another of the university's clinical campuses, the Buffalo General Hospital, to mark the inauguration of postgraduate anesthetic training under Evans' careful scrutiny in 1938 (37). She remained in the city and the department throughout her career.

Concomitantly, under the Evans' aegis, the faculty of anesthetists within the university expanded. In 1937, Dr. Dean Babbage, a future chairman of the department, and Dr. John T. Gabbey, about whom little is known, were appointed assistants in Evans' department (38); 2 years later Mayo Clinic residency-trained Dr. Paul W. Searles entered the department as an associate in anesthesia (39). The stalwart Dr. Durshordwe was elevated to an associate in anesthesia in 1939 (40).

Evans always manifested qualities during his entire career enduringly characteristic of true professionalism—that is, the ability to function dutifully with a degree of above-average competence in his calling and skill day in and day out, year in and year out. As a researcher over 33 years, he managed to produce 29 articles—while never receiving money to support his research. He wrote on many aspects of anesthesia: the necessity to emphasize patient care, inhalation techniques, and oxygen therapy.

Of the first two categories, Evans was unique in his emphasis on patient care. He especially loved children, often spending considerable amounts of his income on toys for his pediatric patients (41). Evans was concerned with how children perceived anesthesia; a pleasant induction for the first operation meant ease with any subsequent surgery. Often he would play a game with the children. They took one breath then Evans took one, the point of the exercise was to see who went to sleep first (42). One 5-year-old tonsillectomy patient who won the contest lovingly saved for over 65 years the five shiny pennies Evans had given her. In the pouch that held them was a note from her mother; "Gift from Dr. Evans, January 25, 1926" (43).

Oxygen therapy remained Evans' overwhelming research interest. Fully a half century after one of Evans' lectures on the subject, one of his former medical students recalled an oxygen cylinder Evans brought to class. Having successfully cannulated a vein, allowing a slow infusion of gaseous oxygen to enter his circulation, Evans declared, "It's bubbling by my ear now" (44).

Indeed, 13 of Evans' professional papers concerned oxygen therapy. Uniquely, he strove hard to develop subcutaneous oxygen therapy as a viable clinical treatment. Beginning with rabbits in the basement of his home, Evans was able to demonstrate improvement in joint mobility in arthritic cases. Often sent patients by the local community of internists when all else had failed, and even then secretly (45), Evans was able to grant symptomatic relief. Making house calls three times a week, he was met at the door with great anticipation (46). Evans tried to convince a skeptical medical community and world of the benefits of his therapy; the result was the 35-mm movie, "Control of Pain and Discomfort With Subcutaneous Oxygen" (47).

Contrary to the then-accepted clinical wisdom, he was convinced that cyanotic patients should and could be treated successfully with high concentrations of oxygen, comparing the use of supplemental oxygen with the use of insulin in hyperglycemic patients (48). He rejected studies of harm done in normal animals by such treatment on the basis that such studies were irrelevant to the care of anoxic patients, and he insisted that supplemental oxygen should be supplied before the development of clinical

cyanosis (49). Evans presented his evidence professionally, and it was soundly based upon his extensive clinical experience (50). However, few physicians were sufficiently impressed to change their traditional oxygen therapy practices.

But less abstract events, the lifestuff of every physician whatever the specialization, provided a different arena for his understanding. No longer well-remembered, the tragic fire in Boston's Coconut Grove nightclub in November 1942 left many of the relatively few survivors suffering from inhalation burns. Evans was called in 38 hours after the ghastly event to administer oxygen to the survivors. In the midst of American involvement in World War II, the army was particularly interested in witnessing the effects of high concentrations of oxygen inspired with positive pressure. Notwithstanding the combination of medical necessity and the victim's trauma, private physicians temporarily obstructed Evans' use of 100% oxygen to treat the victims. Once such traditional obstacles were mastered, however, Evans demonstrated excellent clinical results (51).

For 17 years, anesthesiologists, as well as others of the medical fraternity, argued the highest possible safe percentage of inspired oxygen. At the annual meeting of the New York State Medical Society in 1944, Evans' paper "The War and Oxygen Therapy" again revived the controversy, presenting his excellent clinical results with inspired concentrations far greater than the conventional 60%. He further cited his results with positive pressure delivery in more than 1400 patients, explaining that by utilizing a variable pressure expiratory valve, he was able to administer, by face mask without an endotracheal tube, 4–6 cm of positive pressure during exhalation. In the face of such evidence no one knows how many of his opponents underwent intellectual transformations; but one old opponent, Dr. Alvan L. Barach of Columbia University in New York City, forthrightly acknowledged that high inspired concentrations did in fact benefit certain patients (52).

Research and teaching obligations aside, Evans had throughout his career devoted himself actively to the advancement of anesthesia. In 1915, just a few years after abandoning his Machias practice for appointment to the University of Buffalo, and the year in which his daughter was born, he became a member of the executive committee of the Interstate Association of Anesthetists (53). It is this involvement in organized anesthesia that undoubtably began his 25-year association with McMechan, an association that would catapult Evans to the forefront of the field both scientifically, through the presentation of numerous papers, and politically.



Figure 7. Loving cup awarded to Evans by the International Anesthesia Research Society. (Courtesy of the Evans family.)

A scant year later he became involved with the only national organization, the American Association of Anesthetists, and was admitted as a member at the fourth annual meeting (54). Evans continued his efforts with the organization and was rewarded by being made its president on May 16, 1927. He was involved in this organization's efforts to improve the purity of anesthetic gases through the auspices of the U.S. Department of Agriculture's Bureau of Chemistry (55). After his term of office, Evans continued to serve the organization on its advisory council.

The first annual meeting of the Eastern Society of Anesthetists, a meeting of great importance to Evans, was the forum for presentation of his paper "Blood Pressure Guides and Safeguards in Anesthesia" (56). Along with the pioneers of anesthesiology of the Eastern Seaboard, including Drs. James Gwathmy and Adolf Erdmann, Evans helped create this society to advance regional interests in anesthesia (57). He assumed the organization's presidency in 1928 (58). A year later, his appearance at the presentation of a bust of the father of American anesthetists, William Morton, to the Massachusetts General Hospital placed him, photographically, among the country's standard-bearers for anesthesia (59).

Evans' lengthy association with the Nationallater the International—Anesthesia Research Society began when he became a member of its Research Committee in 1922 (60). Soon he was elected to the

Board of Governors (61) and served as president of the Board for 15 years. The Society grew in membership during his tenure; it sponsored the annual Congress of Anesthetists at the Hotel McAlpin in New York City. Additionally, the Society published the only journal devoted solely to the specialty of anesthesia, Current Researches in Anesthesia and Analgesia. For his devotion to organized anesthesia, Evans was given a 15-inch silver loving cup (Figure 7). It was inscribed:

Presented to John H. Evans M.D. Chairman, Board of Governors International Anesthesia Research Society President Associated Anesthetists of the U.S. and Canada President Eastern Society of Anesthetists As a Token of Deep Appreciation for Meritorious Services in the Organization, Teaching, and Research of the Specialty, as Well as the Development of Nitrous Oxide for Tonsillectomy and Oxygen in the Treatment of Disease by the Associated Anesthetists of the United States and Canada and the International Anesthesia Research Society

In addition to their professional relationship, Mc-Mechan and Evans were close personal friends. Loyal to his sponsor, Evans quickly became a Fellow of the International College of Anesthetists (62), using for the rest of his professional career the letters F.I.C.A. after his name. As the American Society of Anesthetists' (ASA) sponsored certification through the auspices of the American Board of Anesthesiology (63) began to take hold, Evans refused to participate. He relented when he was convinced that the surgeons, through the American Board of Anesthesiology's affiliation with the American Board of Surgery, would not dominate the process (64). Evans made his application for the founders' group of the American Board of Anesthesiology just under the deadline (65).

Upon the death of McMechan, who had been the "originator of organized anesthesia," Evans' leadership skills were sorely tested. After giving a eulogy for his friend at the meeting of the American Society of Anesthetists at the World's Fair in October 1939 (66), Evans, as president of the Board of Governors of the International Anesthesia Research Society (IARS), became saddled with the task of replacing the irreplaceable. As a first step, McMechan's wife and long-time partner Laurette was appointed as an assistant editor of *Current Researches in Anesthesia and Analgesia* and as assistant secretary of the IARS; the latter position she held at the same salary her husband had enjoyed. A new editor was engaged; an editorial board that included Evans helped streamline the transition (67).

It was at this time, in 1940, that Evans decided to open negotiations about the amalgamation of the IARS with the ASA (68). The venture failed, largely because the IARS would have had to eliminate the "associate" membership classification composed of "research workers with doctorates in science" along with "active" members of the dental profession (69) to meet the ASA's rigid membership requirements. Evans was elected president of the International Anesthesia Research Society (70), an office he held into the late 1940s.

In 1943, the Medical Society of the State of New York recognized the specialty of anesthesia by creating a section to study the specific needs and problems of the field within the state. Evans was elected president. He welcomed the society to Buffalo when they held their annual meeting that year (71). It was to be Evans' last elected office, although he continued to practice for another decade.

As always, age and success bred change, including an inevitable yielding to the younger men whom Evans had trained and helped bring into the profession. He was, appropriately enough, replaced as chairman of the University of Buffalo Department of Anesthesiology by Dr. Paul Searles, a graduate of the Mayo Clinic program, sounding the passage of the first era in the development of professional anesthesia, when individuals who had not undergone formalized residency training had dominated. In Buffalo, his legacy lives on, for Evans' second resident, Richard Terry, MD, spent almost 50 years teaching housestaff in Buffalo, vouchsafing his memories of Evans to succeeding generations of anesthesiologists.

Fittingly, Evans died in the hospital he had served so long, the Buffalo General, of heart failure on November 27, 1955. For the latter part of his life he had suffered from angina, which he "cured" with insufflation of subcutaneous oxygen beneath his scapulae. At the time of his death he had been retired only about a year. Mourned by his wife, daughter, and son, he was also lamented by the Buffalo community he served for so long; both local papers ran full-column obituaries with a photograph. Curiously, Current Researches in Anesthesia and Analgesia made no mention of his death; no one immortalized him in

speech at a national meeting, as he had done with McMechan.

By all professional criteria—research, teaching, and civic or professional activism—Evans qualifies as a superior and intrepid figure. During the years when anesthesia was considered a subject unfit for a physician to practice, let alone teach to succeeding generations, he did both: perhaps not with brilliance but with the determination to break new ground. His research was constant in an age when funding was not readily available, useful in disseminating knowledge of anesthesiology, singular in its unique emphasis on inhalation and subcutaneous oxygen therapy in defiance of the conventional wisdom, and rich in anesthesia's tradition of the alleviation of pain. To his patients who received subcutaneous oxygen therapy he was a godsend, and they were often sent to him when all else failed. In the advancement of anesthesiology organizations he stood at the battlements to secure a place of equality for anesthesia for generations to come.

The authors gratefully acknowledge the support of the Evans family.

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Clinical Reports

Aspiration Into the Trachea of a Tracheal T-Tube in a Pediatric Patient

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Key Words: COMPLICATIONS, ASPIRATION OF A TRACHEAL T-TUBE. EQUIPMENT, TUBES—tracheal stents.

Congenital subglottic stenosis accounts for 6%–19% of all congenital laryngeal anomalies, and current reports place acquired subglottic stenosis between 4% and 8.5% of all infants leaving neonatal intensive care units (1,2). Until the early 1970s, subglottic stenosis was managed primarily by tracheotomy and dilatation. Fearon and Cotton reported a mortality rate of 24% among infants and children managed in this manner; thus, alternative approaches to the management of subglottic stenosis have been sought (3). The silicone rubber, tracheal T-tube (E. Benson Hood Laboratories, Inc.) introduced by Montgomery in 1965 (4) has been used increasingly as a stent for the stenotic area as well as a tracheostomal appliance in these patients. Because of the additional advantages of decreased tissue reactivity and the ability of the patients to phonate when these tubes are in place, it is likely that physicians in many diverse specialties such as anesthesiology, emergency medicine, pediatrics, and primary care will encounter this device in the routine and emergency management of such patients.

All physicians should be aware of the unique shape and flexibility of the T-tube because it can lead to unusual airway problems and require quick and unconventional management, as illustrated by the following case.

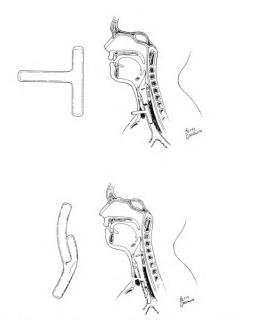
Case Report

A 9-yr-old boy with severe congenital subglottic stenosis that had required more than 40 procedures under general anesthesia, including multiple bronchoscopies with dilation and tracheotomies, underwent placement of a Montgomery T-tube. The procedure and anesthetic course were uncomplicated. On the second postoperative day, the patient began coughing vigorously while secretions in the tube were being suctioned by his father and the external limb of the T-tube was aspirated through the tracheostoma into the tracheal lumen. When he arrived in the operating room (within 20 min) he had severe inspiratory and expiratory stridor, mild cyanosis, and substernal retraction.

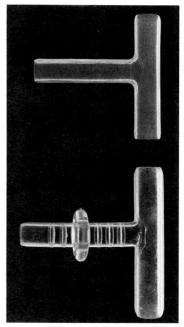
After establishing monitoring and intravenous access, the patient's trachea was topically anesthetized with 2 mL of 4% lidocaine sprayed through the tracheotomy stoma. A 3-mm rigid bronchoscope was introduced through the tracheal stoma and the T-tube was seen lodged in the distal trachea just above the carina (Figure 1). After several unsuccessful attempts to retrieve the T-tube with alligator forceps, a No. 4 Fogarty catheter was introduced beyond the T-tube, the balloon inflated, and the catheter withdrawn. This had to be done multiple times, but eventually the T-tube was visualized at the level of the tracheal stoma and extracted with forceps. Bronchoscopy thereafter revealed no acute tracheal injury. A Portex tracheotomy tube was substituted for the Montgomery T-tube. Throughout the procedure, the patient

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<u>Figure 1</u>. T-tube in normal position (*top*); T-tube aspirated through tracheal stoma (*bottom*).



<u>Figure 2</u>. Pediatric tracheal T-tubes with and without ribbed surface and ring washer.

breathed spontaneously with 100% oxygen being insufflated via the bronchoscope. There were no periods of hypoxemia (oxygen saturation less than 90% as measured by pulse oximetry). He tolerated the procedure well and was discharged later that day in stable condition.

Discussion

Although the soft, flexible silicone rubber T-tube has many advantages in terms of airway stenting, decreased tissue trauma, and maintaining phonation, partial or total airway obstruction can occur and is more difficult to treat than with standard tracheotomy tubes. Rah et al. reported respiratory arrest in a 5-mo-old infant after his Montgomery T-tube became completely obstructed (5). Possible causes for the obstruction included mucus plugging of the T-tube; inability to pass a suction catheter through the distal intraluminal limb; distortion of the distal limb by a large, nonlubricated suction catheter; and partial displacement of the T-tube during suction catheter removal.

Our patient apparently aspirated the entire Montgomery T-tube when a strong negative inspiratory pressure was generated by coughing during suctioning. The flexibility and the small diameter of the external limb of the T-tube allowed for its distal displacement.

The decision to use a topical anesthetic with insufflation of oxygen while maintaining spontaneous ventilation was guided by our inability to guarantee a patent airway in any other manner. Inhalation induction of anesthesia by face mask, commonly used in pediatric patients with foreign body aspiration, was not possible in this patient. The subglottic stenosis would have hindered positive pressure ventilation, and oxygen and inhalation agents would tend to leak from the tracheotomy site. Intravenous induction of anesthesia with a barbiturate, a narcotic, or a benzodiazepine would have depressed ventilation and might have caused complete airway obstruction if positive airway pressure had been applied at the tracheotomy site. Ketamine intravenous induction might have permitted respiration to remain spontaneous, but might have heightened airway reflexes (i.e., reacting to the bronchoscope).

Lack of external stabilization of T-tubes in the airway in children appears to be an important problem. The Montgomery T-tube, which is designed to be indwelling for months, requires a stabilizing mechanism that is long term and atraumatic, and that will not prevent rapid removal of the tube should it become plugged with secretions. Suturing the device to the skin is unsatisfactory and a temporary measure at best. In selected sizes of adult T-tubes (10 mm or greater), the external limb has been recently modified to include a ribbed surface onto which side flanges or a ring washer may be secured and external stabilization established (Figure 2). In light of the complications mentioned above, manu-

facturers should be urged to provide similar modifications on the pediatric-size T-tubes for insertion in the airway.

In conclusion, this report describes a new and potentially lethal complication of flexible silastic T-tubes when used in the management of subglottic tracheal stenosis. Aspiration of the entire tube into the trachea with distal tracheal displacement can be added to the previously described complications of kinking and mucus obstruction of such tubes. Humidification of inspired gases and frequent suctioning are essential during the perioperative period. We recommend that an endotracheal tube of appropriate size and a tonsil forceps be immediately available should it become necessary to remove the T-tube emergently because of obstruction due to aspiration into the trachea. Bronchoscopy with insufflation of

oxygen should be performed immediately should distal displacement of the T-tube occur.

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Vecuronium Neuromuscular Blockade in a Child With Mitochondrial Myopathy

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Key Words: COMPLICATIONS, MITOCHONDRIAL MYOPATHY.

The use of neuromuscular blocking drugs in patients with muscular dystrophy is controversial. Variable responses have been reported, although many patients have uneventful anesthetics with muscle relaxants. However, there are reports of cardiac arrest, masseter spasm, and malignant hyperthermic reactions after the administration of succinylcholine to children with Duchenne-type muscular dystrophy (1,2). Normal responses usually follow the administration of nondepolarizing relaxants (3,4), but a regional curare test has demonstrated prolongation of recovery after d-tubocurarine (5). In a patient with fascioscapular muscular dystrophy, the potency of atracurium was shown to be unchanged, but recovery was slower than normal (6). Unpredictable sensitivity to *d*-tubocurarine occurs in patients with ocular muscular dystrophy (7).

Mitochrondrial disorders resulting from biochemical abnormalities affecting cellular metabolism produce a heterogenous group of illnesses with predominantly central nervous system (mitochondrial encephalopathies) or skeletal muscle (mitochondrial myopathies) involvement (8). There are a few accounts of anesthetic experiences in patients with mitochondrial myopathies (9,10), and none have investigated the response to muscle relaxants.

This case report describes the anesthetic management of a 13-mo-old boy with mitochondrial myopathy requiring general anesthetic for diagnostic biopsy. The sensitivity to vecuronium was assessed by a cumulative dose-response technique (11), and sur-

gical relaxation was maintained with a continuous vecuronium infusion. At the end of the procedure, neuromuscular blockade recovered promptly and was reversed easily with neostigmine.

Case Report

The patient was a 13-mo-old boy scheduled for diagnostic skin, muscle, and nerve biopsies. He had been delivered normally at term after an uneventful pregnancy. Neonatal Apgar scores were not known, but his mother said that he took a long time to breathe and had been difficult to feed since birth. He failed to thrive and at 6 mo of age his height and weight were below the third percentile. Muscle weakness caused delayed motor development and he suffered frequent chest infections. A chest x-ray when he was 10 mo old showed increased bronchial markings. Lactic acidosis was demonstrated and a presumptive diagnosis of mitochondrial myopathy was made.

On elective admission for diagnostic biopsy, he was small, weighed 6.8 kg, and was unable to speak. He had poor muscle tone and could not sit unsupported, but reflexes were intact and there was no muscle wasting. A bone survey assessed age as 3–6 mo. Nerve conduction studies and electromyograms were normal. Capillary blood gas analysis showed a compensated metabolic acidosis (pH = 7.38, Pco₂ = 29 mm Hg, HCO₃⁻ = 17.4 mmol/L, and base deficit = 6.6 mmol/L) and lactic acidosis (lactate = 3.2 nmol/L, pyruvate = 176 μ mol/L, lactate/pyruvate ratio = 18:1).

Arterial oxygen saturation was 97% and serum levels of electrolytes and immunoglobulins, as well as liver function tests, were within the normal ranges. Sweat chloride concentration and 72-h fat absorption were normal. Barium swallow excluded upper gastrointestinal abnormality.

Preoperatively, oral sodium bicarbonate (3 mEq/kg daily) was given to counteract the metabolic acidosis.

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No premedicant drugs were used, and clear fluids were offered up to 4 h before surgery. After routine monitoring devices were applied, anesthesia was induced with 0.1 mg atropine, 5 mg/kg thiopental, and 3 μ g/kg fentanyl intravenously, and a mixture of nitrous oxide and oxygen (2:1) was administered using a modified Ayre's T-piece. Supplemental doses of thiopental, to a total dose of 65 mg, were given during the procedure.

Neuromuscular function was monitored by trainof-four responses using a Grass stimulator and FT-03 force-displacement transducer with a chart recorder. The arm was immobilized in a splint and the ulnar nerve stimulated at 12-s intervals by four supramaximal stimuli with square pulses of 0.2 ms delivered at a frequency of 2 Hz. The response of the adductor pollicis of the thumb was recorded. When a stable train-of-four recording was obtained, a bolus of 0.02 mg/kg vecuronium was administered. At maximum depression of the first twitch (T1) of the trainof-four (as judged by three consecutive T1 responses remaining at the same height), an incremental dose of 0.01 mg/kg vecuronium was given and an infusion of $0.04 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ was begun. When the maximum effect of each successive dose was obtained, a further incremental dose of 0.01 mg/kg was given and the infusion was increased by 0.02 mg·kg⁻¹·h⁻¹.

Once the twitch response was completely abolished, nasotracheal intubation was performed easily with a Portex 4.5-mm outer diameter endotracheal tube with intermittent positive pressure ventilation adjusted to maintain normocarbia, using end-tidal carbon dioxide monitoring. The patient was turned prone and surgery commenced. The vecuronium infusion rate was adjusted to maintain neuromuscular blockade at 95%-100% depression of T1 control height during surgery. After 45 min it was discontinued, and neuromuscular activity was allowed to recover spontaneously. Neostigmine, 0.06 mg/kg, and 0.02 mg/kg atropine were given intravenously when T1 had recovered to 10% of control height. Extubation was performed 9.5 min later, when the child was breathing and moving all four limbs. Arterial blood gas analysis at the end of the vecuronium infusion showed a combined metabolic and respiratory acidosis (pH = 7.23, $Pco_2 = 47$ mm Hg, HCO_3^- = 19.7 mmol/L, base deficit = 8.6 mmol/L). The patient was transferred to the recovery room breathing supplemental oxygen and was warmed with a heating blanket. Recovery was uneventful and the child was discharged home 7 days after surgery.

The biopsy findings supported the diagnosis of mitochondrial myopathy, but the specific enzyme defect could not be identified. One year after surgery, the child developed pneumonia and respiratory failure from which he died.

Examination of the vecuronium dose-response relationship (log dose vs T1% height) showed that the ED₅₀, ED₉₀, and ED₉₅ were 0.029, 0.040, and 0.048 mg/kg, respectively. The vecuronium infusion rate averaged 80 μ g·kg⁻¹·h⁻¹, with a total dose of vecuronium of 0.434 mg (0.064 mg/kg). At the cessation of the vecuronium infusion T1 was 1%, and it took 16 min to recover spontaneously to 10% of control value, with 5%–10% recovery in 5.5 min. After pharmacologic reversal T1 was 94.1% and the T4 ratio was 84.4% within 9.5 min and the trachea was extubated successfully.

Discussion

Mitochondrial myopathies are uncommon forms of muscular dystrophies. They are identified and classified by the detection of specific biochemical abnormalities of mitochondrial enzymes or characteristic morphologic changes in the skeletal muscle: an increase in the number and size of the mitochondria and a ragged red appearance of skeletal muscle fibers when stained with a modified Gomori's trichrome stain. A genetic basis for the defects in intracellular energy metabolism in mitochondrial diseases has been suggested (8,12,13). Deletions of mitochondrial DNA have now been identified in these patients and may provide an explanation for their biochemical and clinical disorders (14,15).

In 1962, Luft et al. (16) first recognized mitochondrial myopathy in a patient with hypermetabolism, but the term is now applied to a group of disorders with heterogenous clinical manifestations (8,17,18). The patient studied was diagnosed clinically as having cytochrome oxidase deficiency (the commonest form of mitochondrial myopathy in infants) because of severe hypotonia, developmental delay, and lactic acidosis. He had no evidence of systemic involvement and cardiac, hepatic, renal, and central and peripheral nervous systems were unaffected. However, frequent chest infections led to terminal respiratory failure, which commonly causes death in infancy or early childhood in these patients.

Anesthetic considerations in patients with neuromuscular disorders relate to the adequacy of respiration, avoidance of cardiac arrhythmias, and abnormal responses to anesthetic agents (19,20). The administration of succinylcholine and halothane to patients with mitochondrial myopathy is not recommended because of an increased risk of malignant hyperthermia (21) and myotonic rigidity (22). The possibility of a sensitivity to nondepolarizing muscle relaxants has been suggested (20). Recent reports of the anesthetic management of patients with mitochondrial myopathy include the safe use of ketamine (23), isoflurane, and atracurium (9,10). This patient had an uneventful anesthetic with thiopental, fentanyl, and vecuronium, followed by an uncomplicated postoperative course.

The dose responsiveness to vecuronium showed an ED₅₀ and ED₉₅ of 0.029 and 0.048 mg/kg, respectively. There is a marked age dependence in the sensitivity to vecuronium, but these requirements are similar to those reported by Meretoja et al. (24) for normal patients of the same age (ED₅₀ and ED₉₅ of 0.031 and 0.057 mg/kg, respectively) during narcotic anesthesia. Infusion requirements were also similar to those of normal children (25). As the dose responsiveness of the patients studied varied widely and the monitoring techniques differed, it is concluded that this patient with myotonic dystrophy showed a normal sensitivity to vecuronium. The recovery and reversal characteristics of neuromuscular blockade in this patient could not be compared directly with studies of normal children after vecuronium using the same monitoring techniques during comparable anesthetic conditions. However, Goudsouzian et al. (26) found that 5%–10% recovery of control twitch took only 2 min in 2-9-yr-old children during halothane anesthesia, suggesting that this patient's recovery (5.5 min) was slower. More recently, Kalli and Meretoja (27) found that the recovery index of infants, monitored electromyographically, could be two or three times longer than that of older children during narcotic anesthesia. Therefore, it is unlikely that recovery in this patient was very different from

The persistent metabolic acidosis must not be ignored in interpreting these responses to vecuronium. Experimental evidence has shown that it increases *d*-tubocurarine (28) but not pancuronium (29) requirements in cats, and does not alter neostigmine antagonism of either (28,29). The relationship of carbon dioxide tension to the rate of recovery from vecuronium blockade has been studied to a limited extent by Gencarelli et al. (30), who showed that induced hypocarbia did not alter the recovery index in humans. Therefore, the combination of a chronic metabolic acidosis and compensatory respiratory alkalosis before surgery may have been an important, but poorly understood, factor in the characteristics of the response to vecuronium in this patient.

This case report describes the anesthetic management of an infant with mitochondrial myopathy using a narcotic and vecuronium technique. No clinical

problems were encountered and the response to vecuronium neuromuscular blockade appeared to be similar to that of normal children of the same age.

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Relief of Causalgia With Prostaglandin E₁ Ointment

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Key Words: PAIN, CAUSALGIA—relief with topical prostaglandin. HORMONES, PROSTAGLANDIN E₁—relief of causalgia.

Causalgia is characterized by an unpleasant burning pain occurring after nerve injuries often caused by crush injuries of the limbs (1,2). The pain is often intractable and is accompanied by sympathetic disorders such as reduced tissue blood flow and perspiration abnormalities. In advanced stages, causalgia may cause muscle atrophy and regressive changes of the skin, nails, and bones. Because of persistent pain, causalgia frequently poses major problems at work and in activities of daily life. Various treatments, including sympathetic blockade (3,4) and neuroelectrotherapy (5), have been attempted for the management of this pain with good therapeutic results. A mechanism by which sympathetic blockade relieves pain is that it increases the tissue blood by inducing vasodilation of the blocked region. Recently, the administration of the vasodilator phenoxybenzamine (6) or a Ca²⁺ channel blocker (7) has been reported to alleviate pain of sympathetic reflex dystrophy. The pain-relieving effects of these agents are considered to be derived also from their vasodilating effects, with a resultant increase in the blood flow to the painful

· Prostaglandin E_1 (PGE₁) increases tissue blood flow and improves the circulatory state by potent vasodilating (8,9) and antiplatelet (10) effects. In this study, we treated a patient with causalgia by topical application of a PGE₁ ointment and observed marked alleviation of pain.

Case Report

The patient was a 54-yr-old man who suffered amputation of the second, third, and fourth digits of the right hand distally to the proximal phalanges in an accident during lathe operation. Intense pain, starting immediately after amputation, involved the entire right hand and centered around the stumps. Healing of the injury was smooth, but the pain gradually intensified, and the area of the pain extended from the right hand to the forearm and the upper arm. The pain, described as continuous burning, fulminant pain, was induced by touch and cold stimulation. Marked swelling, cold sensation, and abnormal perspiration were noted at the site of the pain. Because the pain was not alleviated by the administration of nonsteroidal antiinflammatory analgesics, the patient was referred to our pain clinic 1 mo after the injury, where he had continuous extradural block of the neck with 0.25% bupivacaine and stellate ganglion block with 1% lidocaine that gradually relieved the pain and swelling. After the 20-day treatment, stellate ganglion block was repeated once or twice a week in the outpatient clinic. Three months after the beginning of the treatment, the swelling of the right arm disappeared, and the pain became limited to the amputated digits and surrounding areas.

Topical therapy with PGE₁ ointment was attempted to manage the residual continuous burning pain and increased pain sensitivity. This therapy was approved by the Committee for Human Research at our institution and informed consent was obtained. The PGE₁ ointment, prepared by mixing 400 μ g of PGE₁ crystals with 50 mL of white Vaseline, was stored in a refrigerator and was used within 1 mo of preparation. Six packages each of the ointment and a placebo consisting of Vaseline alone were used for application, once a day, in the order indicated by the predetermined random numbers. The ointment used was applied at and around the site of the pain and the area was dressed with a thin vinyl film to prevent drying. The ointments were applied a total of 12 times according to the double-blind method, and the

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 $\underline{\text{Table 1}}$. Results of Topical Therapy With Prostaglandin $\underline{E_1}$ Ointment

PGE ₁ + Vas	eline ointment	Vaseline ointment alone (control)				
Application No.	Pain-relieving effect	Application No.	Pain-relieving effect			
1	2-	2	+			
4	2-	3	<u>+</u>			
5	2-	6				
7	2∸	8	-			
10	2÷	9	****			
11	2+	12				

PGE₁, prostaglandin E₁; see text for explanation of pain relief scores.

effects of the treatment were evaluated. The pain-relieving effect was assessed according to changes in the visual analog scale (VAS) (10-point scale) and to whether or not pain was induced by compression of the painful site. The treatment was considered to be markedly effective (2+) when the VAS was reduced by 3 points or more, or when tenderness was markedly alleviated; effective (1+) when the VAS was reduced by 1–3 points or tenderness was slightly alleviated; (±) when the pain was slightly alleviated; and (–) when the pain was not decreased.

Table 1 shows the results of the topical therapy with PGE_1 ointment. The VAS before treatment was 3–5, and intense pain was induced by a light compression of the site. The VAS was 0 after each of six applications of the ointment and light compression was tolerated. In the control group treated with Vaseline alone, a slight pain-relieving effect was noted with the first two applications, but no changes in pain were noted at the subsequent four applications. The duration of the pain-relieving effect of the PGE_1 ointment was about 8 h. No side effects were observed.

Discussion

Pain in patients with sympathetic reflex dystrophy such as causalgia is caused as the sympathetic reflex (which normally feeds back negatively to nociceptors in the presence of prolonged pain stimulation) begins to feed back positively to set off a vicious cycle of pain. The sustained sympathetic excitation due to pain stimulation induces peripheral vasoconstriction with resultant regional circulatory disturbances that, in turn, stimulate nociceptors to accelerate the pain. Sympathetic blockade is effective against this vicious cycle of pain, because (a) it interrupts the conduction in sympathetic nerves, the ascending pathway of pain stimulation, and (b) it increases the regional

tissue blood flow. Prostaglandin E_1 ointment probably also alleviates pain by interrupting this vicious cycle of pain with its potent peripheral vasodilating effect. Prostaglandin E_1 is reported also to inhibit the peripheral sympathetic nerves (11), and this action may be involved in its pain-relieving effect.

Prostaglandin E₁ is a pain-enhancer acting on nociceptors, as are other prostaglandins, and it has been shown to increase the pain-inducing effects of agents such as bradykinin, acetylcholine, and histamine (12,13). In this study, however, PGE₁ reduced, rather than enhanced, the pain of causalgia. This finding may indicate that the pain of causalgia is produced by a mechanism different from ordinary pain based on stimulation of nociceptors.

In summary, topical therapy with PGE₁ ointment was effective and safe for the control of pain in a patient with causalgia, suggesting that further studies in a large number of patients should be undertaken to evaluate this pain-relieving effect of PGE₁ in causalgia.

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Unexplained Increases in Serum Creatine Kinase Levels: Its Relation to Malignant Hyperthermia Susceptibility

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Key Words: HYPERTHERMIA, MALIGNANT. ENZYMES, CREATINE KINASE.

Malignant hyperthermia (MH) is an inherited skeletal muscle disorder characterized by hypermetabolism, muscle rigidity, rhabdomyolysis, fever, acidosis, and death if untreated. The syndrome is believed to result from abnormal control of intracellular calcium ions in the skeletal muscle such that, on exposure to certain anesthetics, calcium levels increase and activate contractile processes and biochemical events that support muscle contraction. Although MH is believed to represent myopathy, patients rarely have clinical evidence of muscle abnormalities.

Elevated serum levels of creatine kinase (CK) are a marker of muscle sarcolemmal damage that may occur secondary to trauma, disease, or drugs. The significance of persistently elevated serum levels of CK in the absence of overt myopathy or other causes of muscle damage is uncertain. We describe seven patients with persistently elevated levels of serum CK who were referred to our unit for diagnostic muscle biopsy including testing for MH susceptibility.

Methods

Seven patients with persistently elevated serum CK levels in the absence of neurologic findings on initial examination were referred to Hahnemann University Hospital in the 3 yr between 1986 and 1989 for diagnostic muscle biopsy. All were tested for MH susceptibility by the halothane-caffeine contracture test (1). From January 1986 to November 1987, patients were tested according to a standardized institutional protocol (1). After November 1987, contrac-

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ture testing was performed according to the recently adopted North American MH Group protocol (2). Both protocols determine MH susceptibility by the in vitro contracture response of muscle after exposure to 3% halothane alone and to 2 mM caffeine alone. The normal response to halothane is a contracture less than 0.7 g and to 2 mM caffeine, a contracture of less than 0.3 g.

The patients' histories and findings are presented in Table 1.

Discussion

The major distribution of the CK enzyme is in the skeletal muscle with the MM isoenzyme predominating. Minute amounts of MB fraction have been detected in normal skeletal muscle. Small amounts of CK enzyme are present in the uterus, gallbladder, pylorus, and thyroid and adrenal glands. Very low levels are present in the lungs. The enzyme is absent from the human liver and mature erythrocytes (3).

A host of factors must be considered in correctly interpreting serum CK values. The serum CK levels are lower in children and reach levels normal for adults by about 5 or 6 yr of age. A small but significant decrease occurs with age in men. Women have lower levels than men and also have steadily increasing levels during the day (3). Ideally, measurement of serum levels should be performed soon after the venipuncture, and hemolysis should be avoided.

Abnormal and prolonged exercise markedly elevates serum CK levels with MB fraction demonstrated in the serum of marathon runners (4). Serum CK elevation subsequent to exercise is unpredictable and partially dependent on conditioning. It reaches peak values 14–16 h after exercise and can remain abnormal for several days (5).

Skeletal muscle trauma can increase enzyme levels, as can direct current countershock (6) and electroconvulsive therapy. After operation, a marked and sustained elevation of serum CK levels occurs (7).

Table 1. Patient Histories and Findings

Patient No.	cha	Patient characteristics					C	In vitro testing			
	~	Sex	Weight (kg)	Clinical history	Family histo r y	Physical findings	Serum CK level (U/L)		thane	Caffeine 2 mM	— Muscle histology
1	49	М	90	Muscle cramps and persistently elevated serum CK levels; no history of muscle weakness or muscle pains	Negative	Normal	384-462	2.6 g cor	ntracture MH suso		2+ variation in fiber size and scattered angular fibers
2	34	М	72	Persistently elevated serum CK level; scheduled for inguinal herniorrhaphy	Negative	Left inguinal hernia	350	Normal	Not susc	Normal eptible	Normal
3	59	M	89	Recurrent rectal fistula and elevated serum CK level; had general anesthesia in the past for T & A and fistulectomy without complications	Negative	Degenerative osteoarthritis	373-481	2 g cont	racture MH susc	Normal eptible	Nonspecific changes
4	40	F	70	Incidentally determined elevation of serum CK levels 9 yr ago; had undergone neurologic work-up and deltoid muscle biopsy showed signs of multicore disease	Mother had elevated serum CK level also	No evidence of myotonia	606–2815	Normal	Not susc	Normal eptible	Normal
5	12	М	44	Persistently elevated CK found during evaluation for syncopal episodes; had general anesthesia in the past for myringotomy without complications	Negative	No evidence of muscle disorders	2005	Normal	Not susc	Normal eptible	Mild nonspecific changes
6	16	М		Elevated serum CK level during preoperative evaluation for wisdom teeth extraction	Negative	Upper torso muscle weakness and right arm weakness	900–1300	2.9 g cor	ntracture MH susc	contracture	Variation in fiber size and scattered angular fibers
7	17	F	53	Scoliosis scheduled for posterior spinal fusion; elevated serum CK found during preoperative examination; neurologic evaluation negative	Negative	Marked scoliosis, no evidence of neuromuscular dysfunction	1369	Normal	Not susc	Normal eptible	Normal

CK, creatine kinase; T & A, tonsillectomy and adenoidectomy.

Intramuscular injection of drugs and also oral administration of some drugs can elevate serum CK levels (3). Release of CK from muscle after succinylcholine administration is generally related to the degree of fasciculation and repeat dosage (8). Determination of the serum CK MB isoenzyme provides a sensitive and

specific method for diagnosing acute myocardial infarction (9).

Increased serum CK-MB levels have been found in patients with polymyositis and dermatomyositis without associated cardiac muscle damage (10). Elevations of serum CK-MB and CK-BB levels have been

reported in various muscular dystrophies (e.g., Duchenne, limb girdle) and in neurologic disorders such as ischemic brain infarction, subarachnoid and cerebral hemorrhages, and contusion (11). The presence of CK-MB in the muscle and in the serum of patients with neuromuscular disease is probably related to the presence of immature regenerative muscle fibers (12).

A large number of studies have considered the usefulness of preoperative estimation of serum CK isoenzyme in members of MH-susceptible families. Ellis et al. concluded that estimation of serum CK levels could not be used as a test for predicting susceptibility to MH unless the patient belonged to a family in which high serum CK levels had been shown to correlate with susceptibility to MH (13). Amarnath et al. prospectively studied the value of serum CK screening as a predictor of malignant hyperthermia (14). Two of 1800 patients were MHsusceptible (one by history, one by clinical episode), only one of these had an elevated level of serum CK. Paasuke and Brownell (15) found normal serum CK levels in 34 MH-susceptible individuals as determined by in vitro halothane-caffeine contracture testing. Both of these studies concluded that serum CK level is of no value as a screening test for MH. McPherson and Taylor (16) concluded from a study of 12 Wisconsin families that an elevated serum CK level increases the chance of susceptibility to 94% when, because of family history, the chance of susceptibility is 50%. A normal serum CK level decreases the risk to

A variety of neuromuscular diseases are associated with abnormal halothane contracture test including Duchenne dystrophy, central core disease, Schwartz–Jampal syndrome, and myotonia congenita. They have also been linked to clinical MH (17). One of our MH-positive patients had muscle weakness (patient 6), but did not fit the pattern of any of these disorders. Another patient who proved to be susceptible (patient 1) gave a history of muscle cramps but not myotonia.

It is possible that the MH-positive biopsy results represent a "false-positive" response based on an underlying myopathy characterized by elevated serum CK levels. However, we would then have expected the other patients to be positive too. The false-positive rate in the general population using the North American protocol is not known but is probably less than 5% (unpublished observations, North American MH Biopsy Group). Although only men were MH-positive in this series, there are too few patients to draw conclusions about the significance of this finding. Also, there does not seem to be a greater

elevation of serum CK levels in those who proved to be positive. Our seven patients had no clinical or family history of MH. This is not surprising as MH often does not occur with each anesthetic.

We believe that patients with elevated serum CK levels in the absence of risk factors should have serum CK levels remeasured at suitable intervals to eliminate the effects of trauma or exercise and should undergo a complete neurologic examination. Unexplained persistently elevated serum CK levels in an otherwise healthy individual should alert the clinician to the possibility of MH susceptibility. If a muscle biopsy is advised for diagnostic purposes, in vitro contracture testing with halothane and caffeine for MH susceptibility is also advised.

In summary, seven patients (5 male, 2 female) with unexpected, persistently elevated levels of serum CK were investigated for their susceptibility to MH by in vitro halothane-caffeine contracture testing. Three men but neither of the women were found to be susceptible. The likelihood of MH susceptibility in patients with persistently elevated serum levels of CK is great enough to warrant a thorough neurologic examination together with muscle biopsy for in vitro testing for MH susceptibility.

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Is the Cardiovascular Response to Electroconvulsive Therapy Due to the Electricity or the Subsequent Convulsion?

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Key Words: BRAIN, ELECTROCONVULSION—vascular effects.

Electroconvulsive therapy (ECT) is a frequently used and sometimes lifesaving therapy for patients with major affective disorders. However, the procedure itself is associated with significant cardiovascular morbidity and mortality. Thirty-five cardiac arrests during ECT were reported in California during the period 1974-1983 (1), and cardiovascular mortality remains as high as 0.03% (2). Cardiac morbidity is thought to result from sympathetic and parasympathetic outpouring after the electric shock and the resultant seizure. In a recent study of the hemodynamic response to ECT, we demonstrated mean increases in systolic blood pressure (BP) and heart rate of 155% \pm 3% and 164% \pm 9%, respectively (3). In fact, we have observed systolic BP in excess of 310 mm Hg in previously normotensive patients receiving ECT.

There is general agreement that the cardiovascular changes seen are a normal response to ECT (2,4). What is not clear, however, is whether it is the electric shock or the seizure that causes the hypertension and tachycardia seen after ECT. A recent case may shed some light upon this question.

Case Report

The patient was a 43-yr-old man with a history of ethanol abuse, generalized anxiety disorder, and mixed personality disorder who was admitted to hospital with a 1-mo history of progressive depressive symptoms. The patient's medical history was notable for mild anemia and prostatic nodules. He

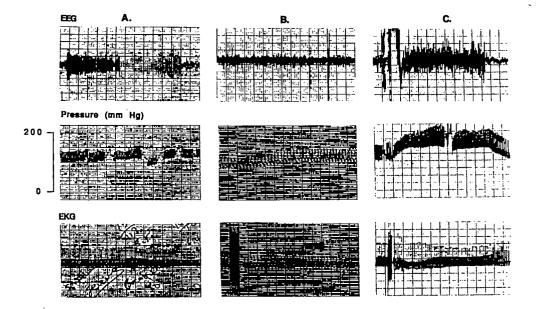
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was otherwise in good general health. During 4 mo of hospitalization, the patient failed to respond to pharmacologic therapy including nortriptyline, haloperidol, lithium, and thorazine. In fact, his depressive symptoms worsened. A therapeutic trial of phenelzine (Nardil) and thiothixene (Navane) was discontinued after 2 wk because severe muscle rigidity, muteness, stupor, and delirium consistent with a partial neuroleptic malignant syndrome developed. Several weeks later a conservator was named and permission was obtained to proceed with electroconvulsive therapy. Electroconvulsive therapy was begun 5 mo after admission. The patient received five unilateral treatments without apparent benefit. He then received 12 bilateral treatments (at a rate of three per week) that resulted in an excellent clinical response. The patient's drug therapy did not change during his course of ECT.

Throughout each ECT treatment session, the patient was monitored with a precordial stethoscope, pulse oximeter, Finapress continuous finger BP monitor, a five-lead electrocardiogram, and an electroencephalogram (one channel, midline forehead to right mastoid). An intravenous catheter was inserted, adequate volume status was assured, and, after baseline measurements, the patient was preoxygenated by mask for 5 min. Anesthesia was then induced with methohexital (70–80 mg, approximately 1 mg/kg). When the patient lost consciousness, ventilation was assisted by mask and a BP cuff was inflated to 300 mg Hg on one calf to isolate the limb (5). The patient then received succinylcholine (70 mg), and, after fasciculations occurred, a mouth guard was placed. He was hyperventilated for 30 s (6). Electroconvulsive therapy was then performed by a psychiatrist using a Thymatron ECT machine (Somatics, Inc.). The ECT machine settings were as follows: charge, 504 mC; current, 0.9 A; frequency, 70 Hz; pulse width, 1.00 mS, and duration, 4 s.

During the course of the patient's ECT sessions, he displayed several events that may shed light on the question of whether it is the electric shock or the



seizure that causes the hypertension and tachycardia seen during ECT. Shown (Figure 1) are the cardiovascular and electroencephalographic responses of this patient during three separate treatments. On the first occasion (A), the patient had a spontaneous seizure immediately after induction of anesthesia with methohexital, before ECT and, therefore, in the absence of an electrical shock. Neither BP nor heart rate changed significantly after the seizure, which lasted 28 s. On the second occasion (B), he received an electroconvulsive shock but failed to respond with a seizure. In this instance, BP increased 50% and there was moderate tachycardia (heart rate increased approximately 25%). On the third occasion (C), the patient received the shock, which resulted in a therapeutic seizure of 57 s. In this case, there was marked hypertension and tachycardia (increases of 50% and 70%, respectively) with a peak pulse pressure of more than 200 mm Hg as well as significant ST segment changes both during and immediately after the seizure. The patient received 14 other ECT treatments during which both a seizure and a cardiovascular response occurred.

Discussion

The present case suggests that it is not the seizure per se that produces the cardiovascular response to electroconvulsive therapy but rather the electrical stimulus or a combination of the stimulus and resultant seizure. During three separate ECT treatments, this patient displayed a spontaneous seizure (without receiving a shock) that was not associated with increases in BP or heart rate, an electroconvulsive shock

Figure 1. Cardiovascular and EEG responses of one patient during three separate ECT treatments. On the first occasion (A), the patient had a spontaneous seizure (top graph, labeled "EEG") immediately after induction of anesthesia, in the absence of an electrical shock. Neither BP (middle graph, labeled "Pressure") nor heart rate (bottom graph, labeled "EKG") changed significantly. On another occasion (B), the patient received an ECT shock but failed to respond with a seizure. In this instance, the BP increased by approximately 50% and the heart rate increased approximately 25%. On the third occasion (C), the patient received a shock that resulted in a therapeutic seizure of nearly 1 min in duration. In this case, there was marked hypertension and tachycardia as significant ST segment changes both during and immediately after the seizure (see text for more details).

that did not produce a seizure but that was associated with significant hypertension and modest tachycardia, and an electroconvulsive shock that produced a seizure associated with marked hypertension, tachycardia, and electrocardiographic changes. We have observed "missed" seizures in response to ECT on other occasions. These patients also exhibited increases in BP and heart rate similar to those described in the present case.

Seizures can occur as a consequence of severe hypertension (7). Seizures can also be an end-stage sign of several conditions in which sympathetic hyperactivity may be another manifestation, such as rabies, drug overdosage or withdrawal, and the use of human recombinant erythropoietin in hemodialysis patients (8). In these conditions, however, hypertension and tachycardia nearly always precede the convulsion. Epileptic seizures, in and of themselves, are not traditionally thought to produce significant tachycardia or hypertension. Contemporary general medical and neurology texts fail to mention tachycar-

dia or hypertension in their discussions of epilepsy or seizures (see, for example, Reference 9).

Electroconvulsive therapy is an important method of treatment of patients with major affective disorders. However, the procedure itself is associated with significant cardiovascular mortality. Studies demonstrating a mortality rate of 3–4 per 100,000 ECT treatments or 3–4 per 10,000 patients treated (10,11) do not support the frequent assertions in the psychiatric literature (e.g., reference 2) that ECT has a lower risk than general anesthesia for other procedures, which now approaches less than 1 per 10,000 anesthetics (12). A large-scale study of 22,210 ECT treatments in Denmark found a death rate of 0.03% (13).

Initially, after the electrical shock in ECT, there is a brief period consisting primarily of increased vagal activity (2,14). This is followed by significant tachycardia and hypertension, which are thought to arise initially by centrally mediated increases in sympathetic activity. This hyperdynamic response is sustained by epinephrine and norepinephrine released from the adrenal medulla (14,15). Serum levels of catecholamines increase 3-15-fold after ECT (14; Partridge et al., unpublished observations). The tachycardia is frequently associated with electrocardiographic abnormalities, including premature ventricular beats (16) and transient T-wave alterations (17,18). Whether the T-wave abnormalities represent cardiac ischemia is controversial (18), but their incidence is higher in patients with preexisting cardiac disease (16).

If a patient responds to ECT with significant tachycardia or hypertension (or has a history of such a response during previous treatments), then it is appropriate to pretreat the patient with a cardioactive agent to blunt this potentially deleterious autonomic response. A recent double-blind, randomized, crossover study supports the use of intravenous esmolol (1 min before anesthetic induction) to blunt the cardiovascular response to ECT (3). Esmolol has a rapid onset and a brief duration and reliably blunts the cardiovascular response to the initial seizure without significantly affecting seizure duration, an important therapeutic variable (19). The additional advantage of esmolol over labetalol is its faster onset and shorter duration. When unacceptable cardiovascular responses to ECT occur unexpectedly, esmolol will rapidly control blood pressure and heart rate.

Many psychiatrists believe that the therapeutic effect of ECT stems from the seizure (2,4). The observations made in this patient, which suggest that at least part of the cardiovascular sequelae of ECT are due to the electrical shock and not to the seizure, suggest an intriguing possibility. It may be possible to

separate the two effects by producing electrical seizure activity in the brain in another way or by altering the characteristics of the electrical stimulus.

The use of electricity to induce seizures has become universal because of its ease of use and its perceived lack of side effects. In patients with significant cardiovascular disease, however, the risks of ECT may be appreciable. Other methods of inducing the therapeutic seizure may, under these circumstances, be safer. In the past, therapeutic convulsions have been induced with camphor (20), insulin (10), and pentylenetetrazole (also known as cardiazol or metrizol) (21). Since this early work, a new class of drugs, benzodiazepine inverse agonists, has been shown to be proconvulsant (22). Their therapeutic efficacy in depression has not been studied. Unfortunately, most chemical convulsants are relatively ineffective in anesthetized animals (22). Interestingly, there are several recent papers suggesting a therapeutic role for isoflurane in severely depressed patients refractory to conventional treatment (23).

As the population ages, and as a greater proportion of patients requiring convulsive therapy develop concomitant heart disease, perhaps a reexamination of the other methods of producing convulsions or a search for new therapeutic modalities for use in patients at the highest risk of cardiovascular morbidity will be appropriate.

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Factitious Prolongation of Bleeding Time Associated With Patient Movement

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Key Words: BLOOD, COAGULATION—prolonged bleeding time.

The bleeding time is the time between the infliction of a small standard cut and the moment when the bleeding stops (1–3). Numerous conditions have been demonstrated to prolong bleeding times (4–6). We report a case of false-positive prolonged bleeding times secondary to patient movement.

Case Report

A 32-yr-old, 50-kg woman, with a documented third ventricle glioma not amenable to operation, was admitted to the hospital with a 12-h history of severe headache, nausea, vomiting, and increasing lethargy. A computed tomography (CT) scan showed hydrocephalus, and radiographs demonstrated an intact ventriculoperitoneal (VP) shunt.

Past surgical history was significant for four previous revisions of the VP shunt over the past 2 yr. In addition, the patient had a craniotomy for partial removal of a cyst and a stereotactic biopsy of her third ventricular tumor, all performed under general anesthesia without difficulty.

Physical examination on admission showed a thin woman, lethargic, oriented to self only, who complained of a headache and had impairment of upward gaze. Blood pressure was 115/70 mm Hg; pulse, 80 beats/min and regular; respirations, 16 breaths/min. Laboratory values included partial thromboplastin time, 29.0 s (normal, 25.9–35.5 s); prothrombin time, 12.8 s (control, 12.6 s; 82% activity); platelet count, 280 × 10³/mm³ (normal, 150–400 × 10³/mm³);

hemoglobin, 13.7 g/dL (normal, 12–16.0 g/dL); and hematocrit, 41.5% (normal, 37.0%–47.0%).

She underwent a successful VP shunt revision under general anesthesia on the day of admission. When the old ventricular catheter was removed, there was some tissue adherent to it that was believed to be a fragment of choroid plexus. When the new catheter was inserted, the cerebrospinal fluid was noted to be blood-tinged initially. Postoperatively, she was awake, oriented to person, place and time; and her headache, nausea, and vomiting had resolved.

The following morning, she was very difficult to arouse. A second CT scan showed an intraventricular hemorrhage in the right occipital horn localized around the ventricular catheter tip and an increase in ventricular size compared with the CT scan on admission. The surgeons performed a percutaneous needle aspiration of the shunt reservoir but were not able to obtain cerebrospinal fluid. Therefore, she was brought to the operating room for emergent VP shunt revision with the assumption that the intraventricular blood around the catheter tip had obstructed the VP shunt. Preoperative medications included nafcillin, phenytoin, and ranitidine. She received no other premedication.

On arrival in the operating room, she was obtunded. The initial bleeding time, determined just before her being taken to the operating room, was prolonged at 24 min. The test was conducted using the modified Ivy method with a Simplate II (Organon Teknika Corp., Durham, N.C.) device to make the incisions and with a blood pressure cuff to maintain venous pressure at 40 mm Hg. Normal results for our laboratory range from 3.0 to 7.5 min. Should the bleeding time be greater than 30 min, the test is automatically stopped at our institution. The bleeding time determination was repeated in the operating room. During the test, the patient made slow constant athetoid movements of the hand and forearm on which the test was being conducted. Several attempts were made to instruct her not to move, but

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she was unable to follow commands. It was uncertain whether these movements were related to the sensory stimulation produced by inflation of the blood pressure cuff or by the test incision, or whether it was related to her neurologic status. The second bleeding time was greater than 30 min. Further examination of the patient failed to find any bleeding from intravenous sites, ecchymosis, or petechiae. The family gave no history of easy bruising or bleeding and said the patient had not taken aspirin preoperatively.

A hematology consultant suggested transfusion of 10 U of platelets and 16 μg (0.3 $\mu g/kg$) of intravenous desmopressin (DDAVP). These were administered. A third measurement of bleeding time was started approximately 15 min after the platelet transfusion was finished and 70 min after administration of DDAVP. The patient again continued her slow constant athetoid movement during the test. The bleeding time was again greater than 30 min. The same laboratory technician had performed all three tests and was confident of the results.

We believed that the constant patient movement during the performance of the test may have falsely elevated the result. We decided to induce anesthesia and to repeat the bleeding time measurement when it became obvious that the third bleeding time was also going to be grossly prolonged. During the final minutes of the third bleeding time, the patient was breathing 100% oxygen. When the test was completed, anesthetic induction was performed with 50 μ g of fentanyl and 400 mg of thiopental administered slowly intravenously until loss of lid reflex, followed by 4.5 mg of vecuronium and 100 mg of lidocaine. Respirations were controlled, and the trachea was intubated. Blood pressure during induction was 105-120 mm Hg systolic and 60-70 mm Hg diastolic, and heart rate was 70–80 beats/min.

The bleeding time immediately after induction of anesthesia was 5.5 min with the patient now motionless. The remainder of the case was uneventful, and the patient did well postoperatively.

Eight and a half months later the patient was readmitted with intermittent lethargy and a history of falling asleep during conversations. Her lateral ventricles were enlarged compared with that shown by her most recent CT scan. She was oriented and cooperative. Bleeding time was 4.5 min.

Discussion

Over the years, many changes have been made in the method of measuring bleeding time since it was introduced by Duke (1). Ivy increased sensitivity by

using a sphygmomanometer to elevate capillary pressure, and therefore, to increase the hemostatic requirement (2). Modifications of the bleeding time included the standardization of the incision depth and length (3).

The bleeding time is prolonged when the level or function of platelets is depressed or when platelets cannot adhere to the wounded vessel. There are numerous causes for congenital or acquired platelet defects (4,5). This patient's platelet count and form on microscopic examination were normal. During her previous hospitalizations, she had normal prothrombin, partial thromboplastin, and bleeding times.

Acquired qualitative platelet defects are common and most frequently are caused by drugs. Nonsteroidal antiinflammatory agents and penicillin-type drugs such as nafcillin can prolong bleeding times (6). The patient's medical history showed that she had not been taking the former but had been given nafcillin, and that she did not have a platelet defect. If she did have an acquired platelet defect, it should have been corrected by the platelet transfusion received in the operating room and should have resulted in a normal bleeding time during the third test, or else, the bleeding time should still have been abnormal on the fourth test also. Platelets develop a functional defect during storage, which may take several hours to correct. When a transfusion of stored platelets is used to treat an aspirin-induced qualitative platelet defect, bleeding times may still not return to normal within 2 h of transfusion; whereas, a transfusion of fresh platelets will return bleeding time to normal within 2 h (7). Therefore, it is very unlikely that the stored platelets transfused to this patient could have made such a marked reduction in bleeding time in the few minutes between the end of the third measurement (45 min after platelet transfusion) and the start of the fourth measurement (50-55 min after the transfusion).

A synthetic analogue of the antidiuretic hormone L-arginine vasopressin, DDAVP has the capacity to increase autologous levels of factor VIII and von Willebrand's factor. Intravenous desmopressin has been used to achieve hemostasis in patients with mild to moderate von Willebrand's disease and in patients with hemophilia A who are undergoing operation. It has also been shown to correct abnormal bleeding times in uremic patients and will shorten the bleeding time in normal subjects (8,9). Intravenous desmopressin has been used for control of surgical hemorrhage in a patient in whom the only significant hematologic abnormality was a prolonged bleeding time (9). It has also been shown to decrease blood loss after cardiac operations (10). Intravenous desmo-

pressin significantly shortens bleeding time within 1 h of transfusion and also significantly increases plasma levels of factor VIII complex by this time (8,9,11). In our patient, DDAVP failed to affect the bleeding time even though 70 min had elapsed between the end of the DDAVP infusion and the start of the third bleeding time.

Our patient had no evidence of coagulopathy. Her localized intraventricular hemorrhage could be explained as being related to the trauma associated with the removal of the initial ventricular catheter with choroidal tissue adherent to it rather than on the basis of coagulopathy.

We believe that in this case the mechanism of prolonged bleeding time was related to patient movement. The muscle contraction associated with her movement could have increased capillary pressure. It has been shown that increasing the capillary pressure with an sphygmomanometer increases the hemostatic requirement (2).

This patient had three bleeding times that were all markedly prolonged, which we believed were due to an increase in the hemostatic requirement caused by patient movement. We proceeded with the anesthetic believing that this would not normally alter the bleeding time (12) and that, if the bleeding time was prolonged secondary to patient movement, the anesthetic might correct the problem. After the patient was anesthetized and motionless, the second bleeding time was 5.5 min. We believe that this represents a case of factitious prolongation of bleeding time caused by patient movement.

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Letters to the Editor

Nasal Endotracheal Tube Change With an Intubating Stylette After Fiberoptic Intubation

Key Words: INTUBATION, TRACHEAL.

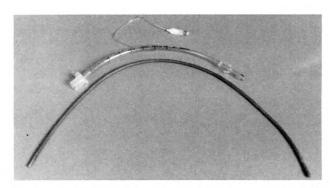
To the Editor:

Fiberoptic laryngoscopy and intubation has been shown to be one of the most effective ways of managing the difficult airway patient. Frequently, the situation arises in which the endotracheal tube needs to be changed in a patient with a history of a difficult intubation. The dilemma is how to change the endotracheal tube successfully while maintaining control of ventilation. The following case report describes such a dilemma and the successful management of it

A 13-yr-old boy with Goldenhar's syndrome, a sporadically genetically transmitted disorder associated with facial asymmetry with mandibular hypoplasia, hypoplastic zygomatic arch, ocular dermoids, vertebral defects, microtia, cleft lip/palate, and occasional cardiac defects (septal defects, tetralogy of Fallot), presented for Harrington rod instrumentation secondary to severe scoliosis. Past medical history included multiple operations for the ocular, otologic, and mandibular defects. The patient had no cardiac lesions.

Physical examination revealed a 162-cm, 40-kg boy with severe scoliosis, a mouth opening of only 2–3 cm, and limited neck range of motion. The uvula could not be visualized. It was decided that awake nasal fiberoptic intubation be performed to secure this very difficult airway. Preoperatively, the patient was given 10 mg intravenous (IV) metoclopromide, 50 mg IV ranitidine, and 0.2 mg IV glycopyrrolate. The oral pharynx was sprayed with Cetacaine, and oxymetazoline (Afrin) was sprayed into the nasal passages. The patient was sedated with 0.1 mg/kg IV midazolam, 2 μ g/kg IV fentanyl, and 1.25 mg IV droperidol. An Olympus LF1 fiberoptic scope (Tokyo, Japan) with an Intertech/Ohio #6.0 cuffed endotracheal tube (Bannockburn, Ill.) cut to a length of 24 cm was successfully passed through the left nasal passage and into the trachea.

After successful awake nasal fiberoptic intubation, general anesthesia was induced. Examination of the nasal endotracheal tube before turning the patient onto the prone position, however, revealed the connector to be only 0.5–1.0 cm from the nares because the tube had been cut to



<u>Figure 1</u>. Pictured is an uncut Intertech/Ohio #6.0 cuffed endotracheal tube and a flexible endotracheal tube changing stylette (Eschmann, Germany).

a length of 24 cm before fiberoptic intubation. This was believed to be unacceptable for the surgery because the patient would be in the prone position. It was therefore decided to change the endotracheal tube and put a longer one in. An intubating stylette (Figure 1, Eschmann, Germany) designed for oral endotracheal tube changes was used to exchange, nasally, the tube for an uncut endotracheal tube. This was done without complication. The patient had an uneventful intraoperative course, was turned supine, awakened, and was easily extubated intraoperatively. The patient had an uncomplicated postoperative course.

To the authors' knowledge, this is the first reported case of an intubating stylette used to change a nasal endotracheal tube. We recommend the use of a flexible endotracheal tube changing stylette. We also recommend that the endotracheal tubes to be used for nasal intubations not be cut until after the trachea is intubated.

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Chin Holders

Key Words: AIRWAY, MAINTENANCE.

To the Editor:

Anesthesiologists trained before the ubiquitous use of endotracheal tubes were taught that one always maintained contact with the patient by holding the anesthesia mask. This teaching applied to all cases regardless of whether a head harness was or was not used. Significant information was obtained; changes in depth of anesthesia as well as patency of the airway could be evaluated. Perhaps most important, one could detect any swallowing that heralded the onset of regurgitation in a patient with an unprotected airway. In addition, the experienced anesthesiologist, with a fifth finger on the branch of the mandibular artery that coursed over the inferior border of mandible, could constantly evaluate the quality of the pulse as well as discern changes in rate and rhythm. The use of chin-support devices during mask anesthesia, such as that recently described by Lee (1), which are designed to free the hands, denies both patient and anesthesiologist the benefit of gathering this valuable information. It should be noted that chin-holding devices, appropriately placed, exert their maximum pressure on an area of the mandible crossed by the artery.

Chin-holding devices (2–5) have almost exclusively been described in the British anesthesia literature. One can only hope that their importation will remain limited.

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Fiberoptic Intubation Facilitated by a Rigid Laryngoscope

Key Words: INTUBATION, TRACHEAL.

To the Editor:

A 60-yr-old man, 180-cm tall, weighing 146 kg, and with a short thick neck, was scheduled for elective coronary artery bypass operation. Evaluation of the airway showed a thyromental distance of 6.0 cm, a mouth opening of 5 cm with good visualization of the palatoglossal and palatopharyngeal arches, and a poor visualization of the uvula. A possible difficult airway/intubation was anticipated, and the difficult airway cart, which included a Pentax FB-18

flexible fiberoptic scope, was brought into the operating room. It was decided by the anesthesia team not to perform an awake fiberoptic intubation initially, but rather to give intravenous midazolam in incremental doses to see if mask ventilation would be possible.

After 0.15 mg/kg of midazolam had been administered intravenously, mask ventilation with slight difficulty was possible and so it was decided to proceed with general anesthesia. Vecuronium (0.1 mg/kg) and fentanyl (25 μ g/ kg) were given intravenously, and after neuromuscular blockade was obtained, oral intubation with a rigid laryngoscope using a McIntosh No. 3 blade was attempted. The laryngoscopist made one attempt, was able to visualize the tip of the epiglottis only, and decided to proceed to fiberoptic laryngoscopy. Two staff anesthesiologists experienced in fiberoptic intubation made several attempts to intubate the patient and were unsuccessful because of massive pharyngeal soft tissue that prevented the tip of the fiberscope from being flexed anteriorly into the glottic opening. Maneuvers such as pulling the tongue forward, jaw thrust, and neck extension proved unsuccessful. Attempts using an Ovassapian fiberoptic intubating airway and a Williams airway intubator were also unsuccessful

As a last resort, one of the assisting anesthesiologists detached a McIntosh No. 4 blade from its handle, inserted it into the patient's mouth, reattached the handle to the McIntosh No. 4 blade, and lifted up the pharyngeal soft tissue. This immediately permitted easy manipulation of the fiberoptic scope into the trachea allowing for an easy fiberoptic intubation.

This successful fiberoptic intubation facilitated by a rigid laryngoscope avoided a tracheostomy in a patient having coronary artery bypass operation. The patient went on to have an uncomplicated perioperative and postoperative course. In the event of a difficult fiberoptic intubation secondary to pharyngeal soft tissue, use of a rigid laryngoscope (McIntosh blade) can provide more room for manipulation of the fiberscope enabling successful intubation that could prove life-saving.

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Pentothal Ready-to-Mix Syringe—A Hazard for the Anesthesiologist

Key Words: ANESTHETICS, INTRAVENOUS—thiopental. EQUIPMENT, syringes—hazards.

To the Editor:

Abbott Laboratories manufactures a Pentothal (thiopental sodium) Ready-to-Mix Syringe (model No. 0074-6243-01) that introduces a risk of hand lacerations to the anesthesiologist using it.

The barbiturate, thiopental, is packed in a glass powder vial marked with a purple cap. To reconstitute the Pentothal, the powder vial is inserted into a plastic injector. Once the yellow cap on the diluent vial is removed, the needle of the injector is inserted through the target area of the rubber stopper on the diluent vial. As illustrated in Figure 1, with the glass diluent vial on a flat surface, the anesthesiologist pushes down on the injector with his hand. This applies pressure to force the diluent into the powder vial to reconstitute the Pentothal.

If the needle of the plastic injector is not placed exactly in the middle of the target area, the needle will not penetrate the stopper to enter the diluent vial. If this misalignment is not detected, the pressure applied to the assembly to force the diluent into the syringe may cause the glass diluent vial to shatter and lacerate the anesthesiologist's hand.

Owing to the personal injury of one of the authors and to an awareness of others having similar problems with this product, an effort was made to assess this problem objectively by surveying 128 Veteran Administration hospitals. A questionnaire was sent to the chief of anesthesia at each hospital asking their experience with the product. None of the hospitals were known to have had an adverse experience with the product before sending out the questionnaires.

Seventy nine (61.7%) of the questionnaires were returned. Results show that 40 of the responding institutions used the product. Eleven institutions reported having had problems with it. Five institutions reported problems with the needle penetrating the target stopper; four reported the powder vial breaking during the reconstitution procedure.

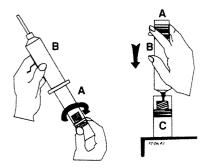


Figure 1. Instructions for assembly of Pentothal Ready-to-Mix Syringe model No. 0074-6243-01. A, powder vial; B, injector; C. diluent vial.

Of the 11 institutions reporting problems, three reported injuries sustained while using the product. Of the three injuries reported, two cases were unspecified lacerations and the third involved a tendon laceration, which resulted in 3 mo of lost work and in a residual decrease in range of motion of the involved thumb.

Anesthesiologists should be able to expect equipment that is safe not only for their patients but for themselves. The results of this survey show that 14% of those responding complained of problems with the product, and 3.8% reported injuries.

It should be noted that Abbott Laboratories makes another Pentothal Ready-to-Mix Syringe (model No. 0074-6420-01), in which the glass diluent vial of model No. 0074-6243-01 has been replaced by a plastic diluent vial. The fact that the plastic model is just as effective, in addition to being much safer, demonstrates that the problem addressed in this survey is readily correctable.

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ECG Artifacts During Cardiopulmonary Bypass—An Alternative Method

Key Words: ANESTHESIA, CARDIOVASCULAR—ECG interference. MONITORING, ELECTROCARDIOGRAPHY—interference.

To the Editor:

Khambatta et al. (1) reported electrocardiographic (ECG) interference from the extracorporeal circuit pump heads during cardiopulmonary bypass and suggested spraying the extracorporeal circuit tubing in the roller heads with atomized tap water to remove the interference transiently.

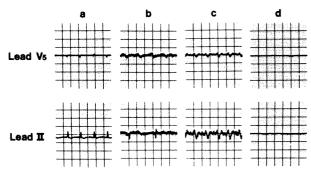


Figure 1. ECG samples before (a, b, c) and after (d) electrical connection between pump housing and arterial temperature port.

We abandoned this technique after noting that smoke appeared from the pump head motor whenever the spray was too liberal. We now use an alternate technique that does not risk damage to the electric motor.

An adhesive ECG electrode is placed on the metal housing of the pump assembly with an ECG lead wire snapped to it. The free male end is then inserted into the perfusate temperature port of the extracorporeal circuit. If the port is in use for temperature monitoring, the male end is attached with tape to the metal sheath of the temperature port. Restoration of a readable ECG trace occurs promptly (Figure 1). Occasionally this maneuver is not successful because, we believe, poor electrical contact exists between the metal sheath of the temperature port and the perfusate.

This method, however, creates an electrical connection between the circulating perfusate of the patient and the grounded housing of the pump assembly, as cautioned by Khambatta et al. Because the connection is maintained only during cardiopulmonary bypass, we do not know of any clinical consequence of microshock should it occur by this route during cardiopulmonary bypass.

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Reference

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Extraction Ratio and Mixed Venous Oxygen Saturation: A False Relationship

Key Words: OXYGEN, UPTAKE AND TRANSPORT.

To the Editor:

I read with interest the article of Trouwborst et al. (1) concerning mixed venous blood gas analysis during normoxic acute isovolemic hemodilution in pigs. With ever-increasing numbers of patients asking that homologous blood transfusions be avoided, I think that this information is particularly timely. Anesthesiologists need to know which indices are predictive of the limits of safe isovolemic hemodilution, and I think that the authors' results certainly have implications in humans. However, when they describe "the strong correlation found between mixed venous oxygen saturation [Svo₂] and extraction ratio [ER]" and depict this relationship in Figure 4, they have made an error of the type described by Archie (2) as "mathematic coupling." They define ER as follows, where Vo₂ = oxygen consumption, CO = cardiac output, Cao₂ =

arterial oxygen content, Cvo_2 = mixed venous oxygen content, Svo_2 = mixed venous oxygen saturation, Sao_2 = arterial oxygen saturation, and O_2 flux = oxygen delivery:

$$\begin{split} \text{ER} \ = \ \frac{\text{Vo}_2}{\text{O}_2 \ \text{flux}} \ = \ \frac{(\text{CO})(\text{Cao}_2 - \text{Cvo}_2)}{(\text{CO})(\text{Cao}_2)} \\ \ = \ 1 - \frac{\text{Cvo}_2}{\text{Cao}_2} \ = \ 1 - \frac{\text{Svo}_2}{\text{Sao}_2} \ = \ 1 - \text{Svo}_2 \end{split}$$

(because Sao_2 approaches 1). Therefore, the graph in Figure 4 is basically Y = 1 - X. The authors used percent and found essentially that Y = 100 - 100X where X or, in this case, Svo_2 , is greater than zero but less than one. In calculating rather than measuring Vo_2 , the graph is predictable without gathering any data at all. I suspect there is a correlation between Svo_2 and ER, but any attempt to describe it using these data is not meaningful.

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In Response:

Indeed, with oxygenation calculations using the indirect Fick method, a source of error can easily be introduced by mathematic coupling of data. Comparing Svo₂ values with ER, mathematic coupling might exist because in calculating the ER, Svo₂ itself is one of the variables. We therefore agree with Dr. Percival that the statement "a strong correlation exists between Svo₂ and ER" deserves further discussion. He suggests that we used in the calculation of the ER the equation

$$1 - \frac{CvO_2}{CaO_2} = 1 - \frac{SvO_2}{SaO_2}$$

which was not the case. In our calculations

$$1 - \frac{1}{Cao_2} = \frac{1}{1 - \frac{Hb \text{ (mixed venous)} \times 1.34 \times Svo_2 + Pvo_2 \times 0.003}{Hb \text{ (arterial)} \times 1.34 \times Sao_2 + Pao_2 \times 0.003}}$$

which includes two factors ignored by Dr. Percival: physically dissolved oxygen fraction and the difference between arterial and mixed venous hemoglobin (Hb) content. Furthermore, Dr. Percival makes the assumption that Sao_2 is almost 100%.

Under normal physiologic conditions (e.g., normal Hb content and normal Sao₂ values) the amount of dissolved oxygen as part of the total arterial oxygen content is

minimal (2.0%–2.5%) and might therefore be excluded in algorithms. However, decreasing Hb content, as in our experiments, at each step of hemodilution, the amount of dissolved oxygen as a percentage of total arterial oxygen content increases and becomes more and more important as one of the variables in calculating the ER.

The difference between arterial $\overline{H}b$ content and mixed venous $\overline{H}b$ content forces one to consider in the algorithm the $\overline{H}b$ values. The equation $\overline{E}R = 1 - Svo_2$ is therefore an oversimplification and a common source of error in several situations (e.g., hemodilution, hypoxemia, hyperoxemia). We do not agree with $\overline{D}r$. Percival that in our presented experiments the relationship between Svo_2 and $\overline{E}R$ was predictable without gathering any data at all. Furthermore, it has been stated that by keeping the range of the independent variable, Svo_2 , as large as possible (as in our study), the effects of coupled error are minimized (1).

Nevertheless, we agree that in part the correlation as presented might be influenced by mathematic coupling because of calculating Vo₂ rather than measuring Vo₂. Meanwhile, some pilot hemodilution experiments have been performed using a totally closed circuit anesthesia machine developed in our department (Physioflex, Weesp, The Netherlands) (2) that measures rather than calculates Vo₂. In these experiments (three animals), a strong correlation has been found between ER and Svo₂, supporting the statement about the correlation between ER and Svo₂.

Adrianus Trouwborst, MD, PhD Elisabeth C.S.M. van Woerkens, MD Department of Anesthesiology Erasmus University Rotterdam and University Hospital Dijkzigt Dr Molewaterplein 40 3015 GD Rotterdam The Netherlands

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Management of Pain

Key Words: BOOK REVIEWS, M. STANTON-HICKS' BOOK.

To the Editor:

The reviews of the books *Pain and the Sympathetic Nervous System* and *Reflex Sympathetic Dystrophy* by Hord (1,2) erroneously state that peripheral nerve stimulator implantation for treatment of RSD is an unproven technique that has not been previously reported in peer-reviewed journals or substantiated by other authors.

The chapter on peripheral nerve stimulation in each book contains references to work by others that has been

reported in peer-reviewed journals. Moreover, the chapter authors' experience with peripheral nerve stimulation has been published in a peer-reviewed article accompanied by an editorial commenting on the value of the technique (3). More to the point, the equipment used and the indication for which it is used is approved by the Food and Drug Administration of the United States.

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Cervical Epidural Abscess After Cervical Epidural Nerve Block With Steroids

Key Words: COMPLICATIONS, EPIDURAL ABSCESS. INFECTION, EPIDURAL ABSCESS. ANESTHETIC TECHNIQUES, EPIDURAL.

To the Editor:

I wish to report the case of a 55-yr-old man in whom an epidural abscess developed in the cervical region after treatment with cervical steroid epidural nerve blocks for cervical radiculopathy.

Approximately 72 h after the third treatment with cervical steroid epidural nerve blocks, the patient had shaking chills and complained of a stiff neck. He was evaluated in the emergency department and was noted to have a temperature of 39.3°C. Examination of the neck showed meningismus.

Myelography demonstrated a complete block of the subarachnoid space at the first thoracic vertebral body. Computed tomography showed that the mass extended to approximately the third cervical vertebral body.

A decompressive laminectomy at the sixth cervical vertebral body was performed. Surprisingly, no cervical epidural abscess was identified. The patient was returned to the intensive care unit where he began to deteriorate neurologically over the next 4 h. A second CT scan showed a persistent epidural mass. The patient was returned to the operating room, and a second laminectomy two interspaces higher was performed. Copious amounts of pus were drained, which subsequently grew out *Staphylococcus aureus*

After the operation, the patient became quadraparetic at a C-6 level bilaterally. Over the following 6 mo, an intensive course of inpatient rehabilitation allowed the patient to regain the ability to walk unassisted and the partial use of his upper extremities.

Epidural abscess after intermittent epidural administration of local anesthetics and steroids is rare (1–5). The diagnosis of epidural abscess should be considered in any patient who has undergone epidural nerve block and in whom increased pain, spasm, new motor or sensory disturbances, and bowel and bladder dysfunction in association with fever subsequently have developed. If epidural abscess is suspected, blood and urine cultures should be taken, and antibiotics that will treat *Staphylococcus aureus* should be started immediately. Emergency computed tomography scan, magnetic resonance imaging, and myelography are indicated to rule out or, if present, determine the extent of epidural abscess. Failure to promptly diagnose and treat a suspected epidural abscess can lead to severe morbidity and mortality.

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Buprenorphine: A κ -Receptor Agonist?

Key Words: ANALGESICS, BUPRENORPHINE.

To the Editor:

We read with interest the article by Carta et al. (1) concerning the effect of nifedipine on morphine-induced analgesia. We congratulate the authors on their very fine paper.

We wish to point out, nonetheless, a possible error. Carta et al. stated in their opening paragraph that buprenorphine is a κ -receptor agonist (1). However, buprenorphine, a relatively new agonist/antagonist analgesic, has a high affinity for and its predominant site of action at the μ -receptors as does morphine (2,3). Rance, in his review of multiple opiate receptors, describes buprenorphine as an analgesic with a clearly defined μ -agonist profile (4). Although buprenorphine does bind to δ - and κ -receptors, activity at these two sites is relatively insignificant (3) and has been demonstrated only in animals. Indeed, buprenorphine has been described as a κ -receptor antagonist: signs of κ -receptor withdrawal develop when buprenorphine is administered (5).

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Errata

Author Index. Vol. 72, No. 2, February 1991, Supplement, p. S338, right column, line 45.

The entry for Conrad P should read "Conard P, see Weller RS."

Edwards WT. Intraspinal opiates in patients receiving podophyllum (letter). Vol. 72, No. 3, March 1991, p. 413.

The first author of Reference 1 should be Conard PF.

Badner NH, Reimer EJ, Komar WE, Moote CA. Low-dose bupivacaine does not improve postoperative epidural fentanyl analgesia in orthopedic patients. Vol. 72, No. 3, March 1991, p. 341.

The journal citation for Reference 13 should be Anesthesia and Analgesia.

Book Reviews

Status of Ketamine in Anesthesiology Edward F. Domino, ed. Ann Arbor, Mich.: NPP Books, 1990, 583 pp, \$95.00

This book represents the publication of the proceedings of the Twenty-Fifth Anniversary of Ketamine Symposium held at the University of Michigan in Ann Arbor on June 19–21, 1989. An international group of clinicians and researchers critically presented the pros and cons of ketamine use today. The breadth of presentation is exhaustive and addresses all aspects of ketamine, from historical and early clinical experience to new basic science developments, including both scientific and review articles.

To minimize an unevenness in text that is invariably present when numerous authors are involved, the editor organized the contents into seven separate sections. Each section addresses a particular aspect of ketamine. The first section on historical and present perspectives emphasizes basic clinical pharmacology. This is followed by sections on biotransformation and pharmacology, analgesic actions, and pharmacokinetics. The fifth and largest section focusing on clinical applications is followed by a section on problems and modern uses, which, in reality, is a more recent update on the newer clinical applications of ketamine in anesthesia. The last section addresses new basic science developments and neuroprotective effects of ketamine.

The quality of reviews and abstracts is consistently high, although lengths may vary considerably. Most sections begin with a few review articles and continue with scientific papers. Some sections are devoted almost entirely to scientific articles such as the pharmacokinetic section and the section on analgesic actions. Others, such as the section on historical and present perspectives, essentially comprise review articles.

The first few articles that discussed the early history of ketamine use, including the "disastrous" British experience in late 1969 and early 1970, were of particular interest. The factors and events that, in retrospect, almost inevitably led to this situation are analyzed and well elucidated. Also described are the efforts and experiences involved in the attempt to reduce the adverse effects of ketamine—the so-called "taming" of ketamine that reduced the initial skepticism and doubts regarding its role in clinical anesthesia. In fact, the book, when viewed as a continuum, provides the reader with a clear understanding of the long and winding road that ketamine has traveled from its initial introduction to its current use in combination with drugs such as propofol.

A major criticism of this book is that the review articles and the abstracts do not always flow in a logical order. Some clarity can be obtained, however, when one follows the major headings and categories. A number of articles in the section on clinical applications deserve mention including the article by Kreuscher, which describes a computersupported infusion model of ketamine-midazolam, also dubbed Computer Tranquanalgesia. A number of novel uses for ketamine were also described including intravenous regional anesthesia, the use of ketamine in a clinic for sedation of mentally handicapped patients undergoing routine gynecologic examinations, and the use of ketamine in combination with the new intravenous anesthetic propofol. Ketamine used for cardiac anesthesia was well addressed in two separate chapters. Each chapter described the results of several studies using ketamine and a benzodiazepine and discussed the role of ketamine in cardiac anesthesia in comparison with other techniques. Other interesting articles include the use of ketamine in the intensive care unit and the administration of low-dose IM ketamine to trauma patients out in the field.

The last section on new basic science developments details research that involves the mechanisms underlying the complex central nervous system actions of ketamine. Two excellent articles by Church review some of the behavioral effects of the dissociative anesthetics and examine the effects of these drugs on central transmitter systems. These articles also discuss and account for the major behavioral changes seen with the drugs.

In summary, this book is a compilation of abstracts and review articles on ketamine that covers a broad spectrum and serves as a testament to the history and current status of ketamine in anesthesiology. It can also be used as a valuable reference by those interested in this unique and fascinating drug. Ketamine finally has found a role in the practice of anesthesiology. This book defines that role and provides the interested reader with numerous ideas and possibilities that have not previously been addressed in one single volume.

Samuel M. Parnass, MD Anthony D. Ivankovich, MD Department of Anesthesiology Rush Medical College Chicago, Illinois Clinical Application of Blood Gases, 4th ed. Barry A. Shapiro, Ronald A. Harrison, Roy D. Cane, and Rozanna Templin, eds. Chicago: Year Book Medical Publishers, 1990, 377 pp, \$36.95.

This book was first published in 1973 when the technology and interpretation of blood gases was still in its infancy. Since that time, it has undergone two revisions, the last of which was in 1982. To keep pace with new technology and information, the text has undergone extensive reorganization, revision, and updating. The book is divided into five major sections.

Section I consists of six chapters which deal with the fundamentals of blood gas interpretation and which review the basic respiratory physiology, physics, and chemistry necessary to understand blood gas data. Section II (eight chapters) discusses blood gas analysis applied to patient care and contains new discussions on the impact of patient temperature and patient metabolic abnormalities on blood gas results. There is also a completely new chapter on blood gases and resuscitation. Section III (five chapters) and section IV (seven chapters) update and expand on material contained in early editions as well as introduce the reader to much of the newer technology now available. Section V consists of two chapters of case studies. Short case studies with blood gas data are presented and interpreted. For maximal educational benefit, the reader is encouraged to interpret the cases with the information provided before reading the authors' analysis.

This book is well written and well organized. Each chapter is divided into subheadings that can be found in the table of contents, and the subheadings are further subdivided into clearly demarcated topics. The structure of the book is such that the more knowledgeable reader may review basic information or jump ahead to advanced topics. On the other hand, the authors take the beginner step by step from the most basic material to the most advanced levels of blood gas interpretation. This user-friendly book is an up-to-date reference that should be in the library of every health-care professional who has a need to know and to understand blood gas interpretation. With the cost of medical texts being what they are, this book should be considered a BEST BUY.

Peter B. Kane, MD Department of Anesthesiology SUNY Health Science Center at Syracuse Syracuse, New York

Respiratory Therapy Equipment, 4th ed. S. P. McPherson and C. B. Spearman, eds. St. Louis: C. V. Mosby, 1990, 624 pp, \$47.95.

No other medical field is more intimately involved in providing mechanical therapeutic measures and life support than respiratory therapy. Proper knowledge of mechanical concepts provides the capability for determining whether clinical problems are physiologic in nature, caused by related medical problems, or arise from the apparatus used in the treatment of the patient. Furthermore, the ability to use and to modify apparatus to meet the special clinical requirements is one of the most critical and rewarding responsibilities of respiratory care personnel.

The approach taken by the author is to first review the principles of physics that must be comprehended to understand fully equipment function. Because respiratory therapy has a great deal to do with gases, the first chapter discusses some of the physics of gases and their effects on the apparatus that respiratory therapists use.

Simpler devices used in respiratory care such as cylinders and piping systems; reducing valves, flowmeters, and regulators; administration devices (i.e., masks, cannulas, and catheters); and controlling devices for blending of air and oxygen are detailed in the following two chapters, and the principles described in these chapters are used as a base to comprehend more complex devices and to analyze the component functions in subsequent chapters dedicated to humidifiers and nebulizers, artificial airways, manual resuscitators, bedside measuring and monitoring devices, adult and pediatric ventilators, and transport and homecare ventilators.

This edition reflects the growth of both the field and the technology used, covers new equipment, and highlights the factors that may be of clinical significance to readers in learning and/or reviewing the aspects of equipment function that relate to their clinical use. Many illustrations and diagrams have been updated or added to improve the visual component of the learning process.

Armando Ferraioli, MSc, PhD Biomedical Engineering Consultancy Cava Dei Tirreni, Italy

The Anesthetic Plan: From Physiologic Principles to Clinical Strategies Stanley Muravchick. St. Louis: Mosby-Year Book, 1991, 425 pp, \$45.00.

Standard textbooks abound in the present literature and there is no dearth of volumes dedicated to specific aspects of the specialty. Therefore, it is exciting to look at this present text because it is unique in its presentation and equally fascinating because it is the result of the laborious work of but one author.

The concept here is to aid the clinical anesthesiologist in providing the best care possible to patients by delving into the backgrounds of applied physiology and pharmacology and then modifying them into a reasonable anesthetic plan. The concept as such is not new. Back in 1948, Dr. Wesley Bourne, one of the foremost anesthetists of his time in Canada, enunciated a similar idea in a paper titled, "At the head of the table." He quoted Eugene M. Landis of Harvard University as follows: "Physiology blends in one direction with cellular, general, and comparative physiology, all leaning towards physics, chemistry and biology. At the other end of the scale organismal physiology, ecology

and human physiology lean toward pathological physiology and medicine, from which, in fact, many of the truly organismal problems and quantitative studies on man have originated." Bourne went on to state that, "We should spare no effort in associating ourselves with and learning from the physiologist, the anatomist, the biochemist, the biophysicist, the pathologist, and the pharmacologist." Muravchick in this volume, some 40 years later, has drawn together, in the light of present knowledge, appropriate aspects of these basic sciences into the realm of anesthesia practice.

After a basic introduction, the book is divided into several chapters that discuss the definition of the anesthetic state, the central nervous system, autonomic homeostasis, neuromuscular function and blockade, cardiovascular function, pulmonary function, hepatic and splanchnic function, renal function and body fluid compartments, and blood and endocrine function. A final chapter describes the anesthesiologist as a consultant with the establishment of priorities to minimize risks as his main concern.

Another unusual aspect of this book is that all 63 figures, drawn to illustrate the text, are original with the author. It must be confessed that, to this aging reviewer, some of these directional figures are somewhat complicated, but with the present youthful readers one can be certain of their comprehension. The information in the 425 pages of this volume has been assiduously researched, as can be determined by the 1168 references that the author notes.

This book is different in its approach to understanding and solving anesthesia problems, and it will be invaluable to those who wish to gain knowledge about why and how daily anesthesia practice is established. Candidates for oral boards will find this book helpful in developing a systematic way to approach a clinical problem.

C. Ronald Stephen, MD Washington University, School of Medicine Chesterfield, Missouri

The 1990 Year Book of Anesthesia

Ronald D. Miller, Robert R. Kirby, Gerard W. Ostheimer, Michael F. Roizen, and Robert K. Stoelting, eds. St. Louis: C.V. Mosby, 1990, 364 pp, \$54.95.

The explosion of medical information both within and outside of the speciality of anesthesiology makes it increasingly difficult for the clinical anesthesiologist to remain current with the literature. The editors of *The 1990 Year Book of Anesthesia* attempt to ease this burden by abstracting and critiquing 319 recent articles collected from a selection of 73 anesthesia-related journals. On the whole the abstracts cover original investigations that are timely to today's practice.

The 12 chapters cover the entire spectrum of anesthetic care from preoperative management through anesthetic techniques to postoperative care. New to this edition is a chapter entitled "Outcomes of Medical Care," which introduces a series of articles that evaluate patient outcome not

only in terms of morbidity and mortality but also in terms of quality of life, quality of care, and cost-effectiveness. The caliber of the selections and the insightful comments of the editor make this section a must. Other portions of the *Year Book* that are particularly well done include the obstetrics portion of chapter 6 (Anesthesia for Certain Types of Surgery), which reviews new developments in peripartum care; chapter 10 (Intravenous Fluid Therapy), which covers such controversial topics as the use of hypertonic saline during volume resuscitation, the indications for perioperative red blood cell transfusion, and the immunologic sequelae of blood cell transfusion; and chapter 3 (Preoperative Evaluation), where the editor brings perspective to the complicated and confusing area of preoperative cardiac evaluation.

There are, however, deficiencies with this text that are inevitable with books of its type. The usefulness of the editors' comments is quite variable. Whereas some provide lengthy, insightful commentaries with references to the literature, others provide brief, superficial comments that add little to the abstract. This is exemplified in article 3-6 for which one editor provides a one-sentence review while another provides a 235-word paragraph that thoroughly dissects and analyzes the article. Also, there are few articles related to the management of postoperative pain, a young and growing area of anesthetic practice. One exception to this is the series of articles on transdermal fentanyl; unfortunately, they are divided between chapter 2 (Pharmacology) and chapter 12 (Management of Pain).

Overall, the 1990 Year Book of Anesthesia is effective in accomplishing its stated goal of reviewing "a wide spectrum of anesthesia-related articles reported in various specialty and other journals worldwide." If used as a guide to the recent literature and not as a text, the book makes a worthwhile addition to the clinical anesthesiologist's library.

David P. Maguire, MD Department of Anesthesiology Thomas Jefferson University Philadelphia, Pennsylvania

Geriatric Surgery: Comprehensive Care of the Elderly Patient

M. R. Katlic, ed. Baltimore: Urban & Schwarzenberg, 1990, 775 pp, \$125.00.

This book, a substantial volume of 775 pages generated by the editor and by 71 other contributors, covers a wide range of geriatric topics. Somewhat surprisingly, it is quite successful, avoiding the pitfalls common to this type of undertaking. Many of the chapters could simply have been generic discussions inserted into a textbook of geriatric medical practice; instead, virtually all 41 chapters were competently written, well documented, and most important, appropriately adapted or modified to deal specifically with considerations important to those who take care of elderly patients. Although some contributors are nationally

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1991:72:719-22

established authorities in their field and others are not well known, the chapters flow from one to the next with a reasonably consistent style and with comparable scope, not always true in an undertaking this ambitious.

The text is divided into four major sections. The first deals with demographic, social, and legal issues; the second, the physiology of aging; the third, the perioperative management; and the last section, a detailed description of the surgical procedures commonly required by this surgical subpopulation. There is some inevitable overlap of content, for example, between the chapter on infectious diseases and age-related immunologic changes. However, the chapters on psychiatric and nutritional changes are relatively unique and of special value to those with a long-term interest in geriatric anesthesia and surgical management. In contrast, the chapter on response to trauma in the elderly patient is clearly a minor revision of a general discussion of trauma and may be better covered in other textbooks. The two chapters that deal primarily with anesthetic management and with preoperative and postoperative care do not break new ground, but are reasonably comprehensive and well referenced. They also pay attention to the current concepts that emphasize the distinctions between aging and age-related diseases and urge appropriate, aggressive diagnostic and therapeutic intervention. They also give much needed emphasis on meticulous and comprehensive attention to the physical details of patient care.

Despite the ambitious scope and prodigious size of this book, this reviewer found it to be a valuable addition to his bookshelf, particularly as a reference source for information on several areas almost never discussed in more limited textbooks on anesthesia for geriatric patients. The convenience of having descriptions of the surgical procedures common in the elderly in the same volume as the chapters

on the physiology of aging will do much to encourage the interested reader to get a better grasp of the overall problem of taking care of these patients. If you have a special interest in the perioperative management of elderly patients, this book belongs in your personal library.

Stanley Muravchick, MD University of Pennsylvania Philadelphia, Pennsylvania

Books Received

Receipt of the books listed below is acknowledged. Selected books from this list will be reviewed in future issues of the Journal.

The Journal solicits reviews of new books from its readers. If you wish to submit a review, before proceeding please send a letter of intent, identifying the book in question, to Dr. Norig Ellison, Department of Anesthesia, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104. The Journal reserves the right of final decision on publication.

Abadir AR, Humayun SG, eds. Anesthesia for Plastic and Reconstructive Surgery. St. Louis: Mosby Year Book, 1991, 467 pp, \$70.00.

Lipnick RL, ed. Studies of Narcosis, written in 1901 by Charles E. Overton, Wood Library-Museum of Anesthesiology, Park Ridge, Ill., 1991, 203 pp,

Lui ACP, Crosby ET, eds. Anesthesia and Neuromuscular Disorders. Volume 5, No. 1 in Problems in Anesthesia series. Philadelphia: J.B. Lippincott, 1991, 177 pp, \$30.00 individual issue, \$70.00 subscription to quarterly publication.

Philip JH. Gas Man, Understanding Anesthesia Uptake and Distribution in Anesthesia and Analgesia. 2nd ed. Chestnut Hill, Mass.: MedMan Simulations, 1991, \$245.00 single copy or \$645.00 Site-License; Macintosh compatible program and tutorial text.

Stanley TH, Ashburn MA, Fine PG, eds. Anesthesiology and Pain Management. Boston: Kluwer Academic Publishers, 1991, 384 pp, \$130.50.

Stehling LC, ed. Perioperative Autologous Transfusion. Proceedings of a National Conference. Arlington, Va.: American Association of Blood Banks, 1991, 177 pp, \$30.00.

A Guide for Authors

Manuscripts should be sent to:

Ronald D. Miller, MD Editor-in-Chief Anesthesia and Analgesia 3497 Sacramento Street San Francisco, CA 94118

Editorial Policies

Anesthesia and Analgesia, the oldest publication for the specialty of anesthesiology, is the official voice of the International Anesthesia Research Society. It publishes original articles, clinical reports, technical communications, review articles, and letters to the editor.

All papers are reviewed by three or more referees. Acceptance is based on significance, originality, and validity of the material presented. Only one copy of an article not accepted for publication will be returned to the author.

The submitted manuscript should be accompanied by a covering letter that includes a statement to the editor about all submissions and previous reports that might be regarded as prior or duplicate publication of the same, or very similar work. The title page and abstract of such material should be included with the submitted manuscript to help the editor decide how to deal with the matter.

Manuscripts must be prepared and submitted in the manner described in "Uniform Requirements for Manuscripts Submitted to Biomedical Journals," reprinted in *The New England Journal of Medicine* 1991;324:424-8.

No manuscripts describing investigations carried out in humans will be accepted for publication unless the text states that the study was approved by the authors' institutional human investigation committee and that written informed consent was obtained from all subjects or, in the case of minors, from parents. No manuscript describing investigations in animals will be accepted for publication unless the text states that the study was approved by the authors' institutional animal investigation committee.

Human subjects should not be identifiable. Do not use patients' names, initials, or hospital numbers.

Authors and their typists should use the checklist given below for preparation of manuscripts:

General

☐ Original articles describe in 3000 words or less clinical or laboratory investigations. □ Clinical reports describe in 1000 words or less either new and instructive case reports or anesthetic techniques and equipment of demonstrable originality, usefulness, and safety. ☐ Technical communications are papers that deal with instrumentation and analytic techniques. ☐ Review articles of 2500 to 4000 words collate, describe, and evaluate previously published material to aid in evaluating new concepts. ☐ Letters to the editor, less than 300 words in length, include brief constructive comments concerning previously published articles or brief notations of general interest. The manuscripts must be doublespaced, and a title and three copies must be provided. □ Type manuscripts on white bond paper, 216 by 279 mm (8½ by 11 in.) or ISO A4 (212 by 297 mm) with margins of at least 25 mm (1 in.) using double-spacing throughout. ☐ Begin each of the following sections on separate pages: title page, abstract and key words, text, acknowledgments, references, tables (each table, complete with title and footnotes, should be on a separate page), and legends. Type only on one side of the paper and number pages consecutively, beginning with the title page. Type the page number in the upper right-hand corner of each page.

Submit original plus three copies of the manuscript and four sets of
figures in a heavy paper envelope. Submitted manuscripts should be
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to reproduce previously published materials or to use illustrations
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- A short running head of no more than 40 characters (count letters and spaces) placed at the bottom of the title page and identified;
- ☐ First name, middle initial, and last name of each author, with highest academic degree(s); each listed author must (a) have participated in the work to the extent that he or she could publicly defend its contents; (b) have read the manuscript before its submission for publication; and (c) be prepared to sign a statement to the effect that he or she has read the manuscript and agrees with its publication;
- ☐ Name of department(s) and institution(s) to which the work should be attributed;
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Abstract and Key Words

- ☐ The second page should carry an abstract of not more than 150 words. (Abstracts are not needed for Clinical Reports.)
- ☐ The abstract should state the purposes of the study or investigation, basic procedures (study subjects or experimental animals; observational and analytic methods), main findings (give specific data and their statistical significance, if possible), and the principal conclusions. Emphasize new and important aspects of the study or observations.
- ☐ Define all abbreviations except those approved by the International System of Units.
- □ Key (indexing) words: Below the abstract, provide (and identify as such) 3 to 10 key words or short phrases that will assist indexers in cross indexing the article.

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- ☐ The text of observational and experimental articles is usually—but not necessarily—divided into sections with the following headings: Introduction, Methods, Results, and Discussion.
- ☐ Case reports, reviews, and editorials do not require the above
- ☐ Introduction: Clearly state the purpose of the article. Summarize the rationale for the study or observation. Give only strictly pertinent references and do not review the subject extensively.
- ☐ Methods: Describe the selection of observational or experimental subjects (patients or experimental animals, including controls) clearly. Identify the methods, apparatus (manufacturer's name and address in parentheses), and procedures in sufficient detail to allow other workers to reproduce the results. Give references to established methods, including statistical methods; provide references and brief descriptions for methods that have been published but are not well known; describe new or substantially modified methods, give reasons for using them, and evaluate their limitations.

☐ Identify precisely all drugs and chemicals used, including generic name(s), dosage(s), and route(s) of administration.	Illustrations ☐ Submit four complete sets of figures. Figures should be in black and
☐ Results: Present the results in logical sequence in the text, tables, and illustrations. Do not repeat in the text all the data in the tables and/or illustrations; emphasize or summarize only important observations.	white only and be professionally drawn and photographed; free- hand or typewritten lettering is unacceptable. Note: Art work of published articles will not be returned.
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Examples: 1. Standard journal articles (List all the authors when six or less; when seven or more, list only the first three and add et al.) Rigler ML, Drasner K, Krejcie TC, et al. Cauda equina syndrome after continuous spinal anesthesia. Anesth Analg 1991;72:275-81.	☐ When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, identify and explain each one clearly in the legend.
Personal author(s) of books and monographs Eisen HN. Immunology: an introduction to molecular and cellular	Abbreviations
principles of the immune response. 5th ed. New York: Harper and Row, 1974.	☐ At first mention in text, spell out in full and follow immediately with the abbreviation (enclosed within parentheses).
3. Chapter in a book Weinstein L, Swartz NM. Pathogenic properties of invading microorganisms. In: Sodeman WA Jr, Sodeman WA, eds. Patho-	Do not synthesize new or unusual abbreviations. When many abbreviations are used, include all in a box of definitions at the start of the article.
logic physiology: mechanisms of disease. Philadelphia: WB Saunders, 1974:457–72.	☐ Consult the following sources for abbreviations: 1. CBE Style Manual Committee. Council of Biology Editors style manual: a guide for authors, editors, and publishers in the
Tables	biological sciences. 5th ed. Bethesda, Maryland: Council of Biol-
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For surgical procedures 90 minutes or longer...

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Long-acting muscle relaxation without vagolytic effects¹

- Does not cause elevation of heart rate or blood pressure.²
- Recommended when cardiovascular stability is desired.³
- A useful alternative to pancuronium in patients where tachycardia is best avoided.⁴
- Provides good to excellent intubating conditions within 2.5 to 3.0 minutes.

See following page for brief summary of prescribing information.





Before prescribing, please consult complete product information, a summary of which follows:

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND

CONTRAINDICATIONS: None known.
WARNINGS: ARDUAN® (PIPECURONIUM BROMIDE) FOR INJECTION SHOULD BE WARNINGS: ARDUAN® (PIPECURONIUM BROMIDE) FOR INJECTION SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EYPERIENCED CLINICIANS WHO ARE FAMILIAR WITH THE DRUG'S ACTIONS AND THE POSSIBLE COMPLICATIONS OF ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND AN ANTAGONIST ARE WITHIN IMMEDIATE REACH. IT IS RECOMMENDED THAT CLINICIANS ADMINISTERING LONG-ACTING NEUROMUSCULAR BLOCKING AGENTS SUCH AS ARDUAN® EMPLOY A PERIPHERAL NERVE STIMULATOR TO MONITOR DRUG RESPONSE, NEED FOR ADDITIONAL RELAXANT, AND ADEQUACY OF SPONTANEOJS RECOVERY OR ANTAGONISM. In patients with myasthenia gravts or myasthenic (Eaton-Lambert) syndrome, small doses of non-depolarizing neuromuscular blocking agents may have profound effects. Shorter-acting muscle relaxants than ARDUAN® may be more have profound effects. Shorter-acting muscle relaxants than ARDUAN® may be more

PRICAUTIONS: General: Since ARDUAN® has little or no effect on the heart rate, the drug will not counteract the bradycardia produced by many opioid anesthetic agents or vogal stimulation. Consequently, bradycardia during anesthesia may be more common with ARDUAN® than when a muscle relaxant (such as pancuronium) which exerts vagolytic action

Remal Failure: ARDUAN®, in the dose of 70 µg/kg actual body weight (ABW), has been studied in a limited number of patients (n=20) undergoing renal transplant surgery recently dialyzed in preparation for cadaver renal transplant. The mean clinical duration (injection to 25% recovery) of 103 minutes was not judged prolonged; however, there was wide inclindful variation (30 to 267 minutes). ARDUAN® has not otherwise been studied in patients with renal failure (for elective or emergency non-renal surgery). Because it is primarily excreted by the kidney, and because some shorter-acting drugs (vecuronium and atrocurium) have a more predictable duration of action in patients with renal dysfunction, ARDUAN® should be used with earth caution in patients with renal failure.

Increased Volume of Distribution: Conditions associated with an increased volume of distribution, eg, slower circulation time in cardiovascular disease, old age, or ede states, may be associated with a delay in onset time. Because higher doses of ARDUAN® may produce a longer duration of action, the initial dose should not usually be increased in se patients to enhance onset time; instead, more time should be allowed for the drug to achieve maximum effect.

Hepatic Disease: There are no data on dosage requirements, onset, duration, or pharmacokinetics in patients with moderate or severe hepatic dysfunction and/or biliary obstruc-tion. This should be considered in selection of muscle relaxants for use in these patients.

ton. This should be considered in selection of muscle relaxants for use in these patients.

Obsetty: The most common patient condition associated with prolonged clinical duration was obestly, defined as 30% or more over ideal body weight (IBW). Clinical study subjects were dosed on the basis of actual body weight, which may have contributed to the higher incidence of prolonged duration. It is therefore recommended that dosage be based upon ideal body weight for height in obese patients.

Mailignant Hyperthermia (MH): Human malignant hyperthermia has not been reported with the administration of ARDUAN®. Because ARDUAN® is never used alone and

because the occurrence of malignant hyperthermia during anesthesia is possible even in the absence of known triggering agents, clinicians should be familiar with early signs, confirmatory diagnosis, and treatment of malignant hyperthermia prior to the start of any anestheric. in an animal study in MH-susceptible swine (n=7), the administration of ARDUAN® was not associated with the development of malignant hyperthermia.

Central Nervous Systems ARDUAN® has no known effect on consciousness, the pain

threshold, or cerebration. Therefore, administration must be accompanied by adequate

Drug Interactions: ARDUAN® can be administered following recovery from succinylchore when the latter is used to facilitate endotracheal intubation.

The use of ARDUAN® before succinylcholine, in order to attenuate some of the side effects

of succinylcholine, is not recommended because it has not been studied.

There are no clinical data on concomitant use of ARDUAN® and other non-depolarizing

neuromuscular blocking agents.

Inhalational Anesthetics: Use of volatile inhalation anesthetics has been shown to enhance the activity of other neuromuscular blocking agents on the order of enflurane > isoflurane > halothane. No definite interaction between ARDUAN® and halothane, as used clinically, has been demonstrated. Use of isoflurane in one study of 25 patients resulted in an increase in mean clinical duration by 12%. In another study of 25 patients first anesthetized with enflurane for 5 minutes or more, the mean clinical duration was increased by 50%. Therefore, a prolonged clinical duration following initial or maintenance doses and pro-longed recovery from neuromuscular blocking effect of ARDUAN® should generally be antic-ipated with enflurane > isoflurane > halothane.

Antibiotics: Parenteral/intrapertoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis; aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamkin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; collstin; and sodium collstimethate.

Others Experience concerning injection of quinidine during recovery from use of other mus-de relaxants suggests that recurrent paralysis may occur. This possibility must also be con-sidered for ARDUAN®. ARDUAN®-Induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (car), in addition, experience with other drugs has suggested that acute (eg, diarrhea) or chronic (eg, adrenocortical insufficiency) electrolyte imbalance may alter neuromuscular blockade. Since electrolyte imbalance and acid-base imbalance are usually mixed, either enhancement or inhibition may occur. Magnesium salts, administered for the management of toxemia of pregnancy. may enhance neuromuscular blockade.

Drug/Laboratory Test Interactions: None known. **Cardinagenesis, Mutagenesis, Impairment of Fertility:** Studies in animals have not been performed to evaluate carchogenic potential or impairment of fertility. Mutage studies (Ames test, Sister Chromatid Exchange) conducted with ARDUAN® revealed no

mutagenic potential.

Pregnancy Category C: A teratogenicity study has been conducted in rats using intravenously administered doses of ARDUAN® approximating the clinical dose in humans (50 µg/kg). No teratogenic effects were observed in this study. An embryotoxic effect (secondary to maternal texicity) was observed at the highest dose administered (50 µg/kg) as demonstrated by an Increase in earlier feet laresorptions. There are no adequate and well-controlled studies in pregnant women. ARDUAN® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Obstetrics (cesarean section): There are insufficient data on placental transfer of ARDUAN® and possible related effect(s) upon the recorde following cesarean section delivery. In addition, the duration of action of ARDUAN® exceeds the duration of operative obstetrics (cesarean section). Therefore, ARDUAN® is not recommended for use in patients

undergoing C-section. **Pediatric Use:** Infants (3 months to 1 year) under bolanced anesthesia (2 studies in 52 infants), or halothane anesthesia (1 study in 29 Infants), manifest striilar dose response to ARDUAN® as do adults on a μg/kg ABW basis. Children (1 to 14 years) under balanced anesthesia (4 studies in 57 children), or halothane anesthesia (2 studies in 29 children), may be less sensitive than adults. These conclusions come from studies involving titrating patient response by the incremental method to approximately 1.2 times ED_{ss}. There are no data on either onset time or clinical duration of larger doses in infants or children. There are no data on maintenance dosting in infants and children. Pharmacokinetic studies in infants and children. dren have not been performed; therefore no pharmacokinetic modeling of incremental dos-ing can be attempted. The use of ARDUAN® in neonates and infants below 3 months of age has not been investigated. Antagonism has not been systematically studied in infants or childran. However, usual clinical doses of neostigmine administered following significant levels of spontaneous recovery (recovery of T₁ to more than 50% of control) produced complete antagonism of residual neuromuscular block in less than 10 minutes in the majority of cases

ADVERSE REACTIONS: The most frequent side effect of non-depolarizing blocking ts as a class is an extension of the drug's pharmacological action beyond the time period needed for surgery and anesthesia. Clinical signs may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insuffi-

clency or apnea. This may be due to the drug's effect or inadequate antagonism.

The following listings are based upon U.S. clinical studies involving nearly 600 patients utilizing a variety of premedications, varying lengths of surgical procedures, and various anesagents.

Adverse experiences in greater than 1% of cases and judged by the investigator to have a possible causal relationship: clinically significant hypotension (2.5% of cases); clinically significant brodycardia (1.4% of cases).

Adverse experiences in less than 1% of cases and judged by the investigator to have a possible causal relationship:

Cardiovascular: hyportension, myocardiol ischemia, cerebrovascular accident, thrombo-sis, atrial fibrillation, ventricular extrasystole.

Metabolic and Nutritionals increased creatinine, hypoglycemia, hyperkalemia.

Musculoskeletal: muscle atrophy, difficult Intubation. Nervous: hypesthesia, CNS depression.

Respiratory: dyspnea, respiratory depression, laryngismus, atelectasis.

Skin and Appendages: rash, utricaria.

Uragenited System: anutria.

HOW SUPPLIED: 10 mL vials containing 10 mg lyophilized pipecuronium bramide. Boxes of 6 (NDC 0052-0446-36) 10 mL vials containing 10 mg lyophilized pipecuronium bramide and 10 mL vials containing bacteriostatic water for injection, USP. Boxes of 6 (NDC 0052-0446-36).

0446-37)

Storage: 2°-30°C (36°-86°F). Protect from light.

After Reconstitution: When reconstituted with bacteriostatic water for injection, USP:
CONTAINS BENZYL ALCOHOL, WHICH IS NOT INTENDED FOR USE IN NEWBORNS.
Use within 5 days. May be stored at room temperature or refrigerated.

When reconstituted with starlie water for injection or other compatible IV solutions: Refrigerate vial. Use within 24 hours. Single use only. Discard unused portion.

REFERENCES

Data on file.
 Foldes FF, Nagashima H, Nguyen HD, Duncalf D, Goldiner PL. Neuromuscular and cardiovascular effects of pipecuronium. Can J Anaesth. 1990;37(5):549-555.
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 Tassonyl E, Neidheart P, Pittet J-F, Morel DR, Gemperle M. Cardiovascular effects of pipecuronium and panauronium in patients undergoing coronary artery bypass graffling. Anesthesiology. 1988;69(5):793-796.

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MARCH 1991

The Osler Institute Anesthesiology Boards Review Course

July 6-11, 1991 – Chicago §September 30-October 5, 1991 – Tampa

Now offering §60 hours of mock oral exams limited to 90 participants

Co-sponsored by the University of Washington

OBJECTIVES

After this program attendees should:

- Have improved basic and clinical anesthesia knowledge
- Be better organized for further study of anesthesiology
- Be prepared to take written and oral exams

METHODS

- HOME STUDY MATERIALS consisting of a syllabus and assignments with questions and answers
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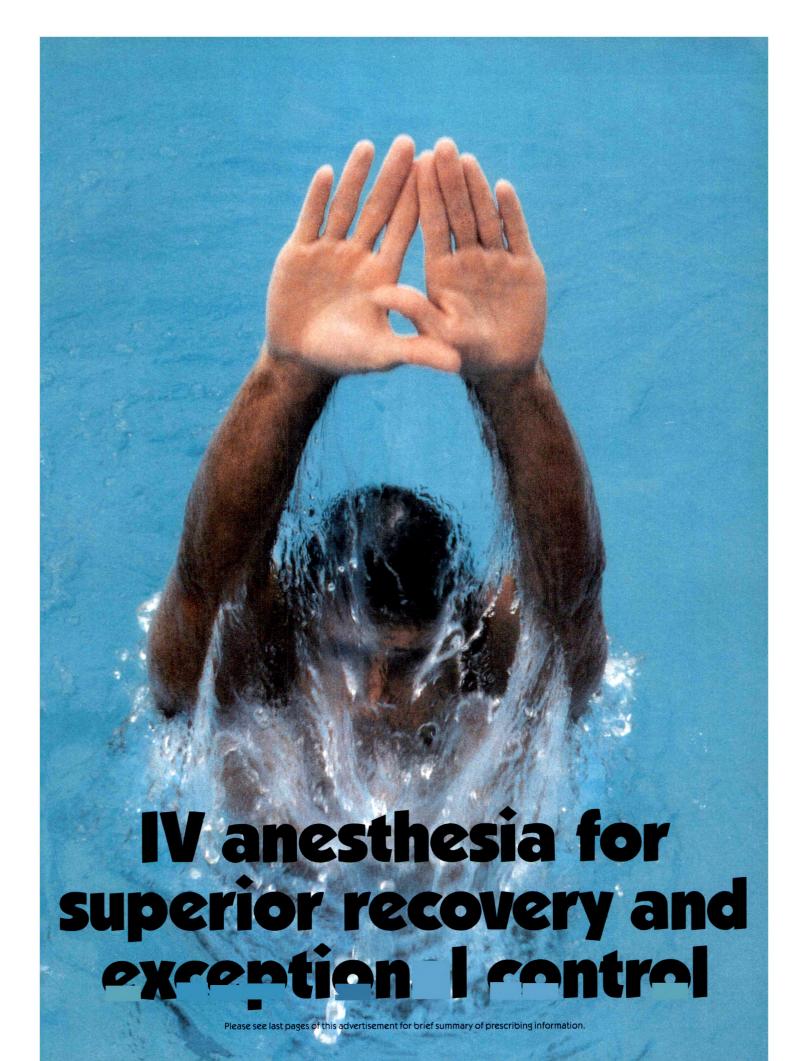
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Superior exceptional



Mean postanesthesia recovery times (min)1		
		Thiopental/ isoflurane
Duration of anesthesia	85*	57
Response to commands	3.5*	6.1
Fully oriented	5.5	9.4
Able to tolerate fluids	61*	130
"Ready" for discharge	138*	206

-adapted from Korttila et al, p A564

"Statistically significant (P < .05). Measurements taken from time of discontinuation of all maintenance anesthesia.

 Majority of patients are generally awake, responsive, and oriented within 8 minutes

recovery and anesthetic control

Significantly less nausea and vomiting than with thiopental/isoflurane

	DIPRIVAN	Thiopental/ isoflurane
Wetchler ² Nausea/vomiting	(n = 20) 20%	(n = 20) 65%
Sung et al ³ Nausea/vomiting	(n = 49) 8.1%	(n = 50) 30%

As part of a balanced anesthetic technique, DIPRIVAN is a cost-effective alternative to thiopental/isoflurane for induction and maintenance.

Please see last pages of this advertisement for brief summary of prescribing information.

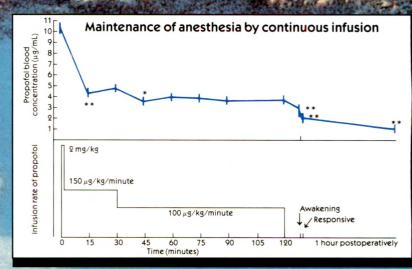
For induction and maintenance





Maintenance of anesthesia as easily controlled as with isoflurane

■ Steady state blood concentrations are proportional to rate of administration



-adapted from Herregods et al, p 3644

*Significant difference (P< .05) from previous value. **P< .02. (Mean and SEM values are shown.)

After a loading dose of 2 mg/kg, anesthesia was maintained with 150 μ g/kg/min for 30 minutes—then 100 μ g/kg/min for 90 minutes.⁴

- Total body clearance exceeds estimates of hepatic blood flow⁵
- No active metabolites produced

As with most an esthetic agents, clearance rate of DIPRIVAN decreases in elderly patients.

recovery and anesthetic control

Hemodynamic effects are controllable and dose-dependent

- Blood pressure (BP) predictably decreases on induction (sometimes > 30%) but is within acceptable ranges for healthy individuals*
- Hemodynamic effects during induction are generally more pronounced than with traditional IV induction agents

After initial decreases in BP following induction, hemodynamics return toward baseline

The cardiovascular effects of DIPRIVAN may be increased in patients who have received sedative or narcotic premedications.¹

DIPRIVAN is not a narcotic agent When used with N_2O/O_2 for maintenance, supplementation with IV analgesic agents is generally required; muscle relaxants may also be required.

Strict aseptic techniques must always be maintained while handling DIPRIVAN. DIPRIVAN is a single-use parenteral product and contains no antimicrobial preservatives. DIPRIVAN Injection should be prepared for use just prior to initiation of each individual anesthetic procedure. DIPRIVAN Injection should be drawn into sterile syringes immediately after ampules are opened. Administration should commence promptly and be completed within 6 hours after the ampules have been opened.

*Elderly, debilitated, and/or hypovolemic patients, and those rated ASA III/IV, may have more profound adverse cardiovascular responses.

†Induction dose requirements may be reduced.

Please see last pages of this advertisement for brief summary of prescribing information

For induction and maintenance

MYR



Superior recovery and exceptional anesthetic control

As part of a balanced anesthetic technique, DIPRIVAN is a cost-effective alternative to thiopental/isoflurane for induction and maintenance.

- Significantly improved speed and quality of recovery compared with thiopental/isoflurane
- Significantly less nausea and vomiting than with thiopental/isoflurane
- As convenient and as easily controlled as isoflurane for maintenance of anesthesia

References: 1. Korttila K, Faure E, Apfelbaum J, Ekdawi M, Prunskis J, Roizen M. Recovery from propofol versus thiopental-isoflurane in patients undergoing outpatient anesthesia. *Anesthesiology*. 1988;69(3A):A564. Abstract. 2. Wetchler BV. A comparative evaluation of recovery following anesthesia with Diprivan® (propofol) by intravenous infusion versus Diprivan® followed by isoflurane versus thiopental sodium followed by isoflurane for short surgical procedures. Data on file, Stuart Pharmaceuticals, Wilmington, Delaware. 3. Sung YF, Reiss N, Tillette T. The differential cost of anesthesia and recovery with propofol-nitrous oxide anesthesia versus thiopental-isoflurane-nitrous oxide. *Anesth Analg.* 1990;70:S396. Abstract. 4. Herregods L, Rolly G, Versichelen L, Rosseel MT. Propofol combined with nitrous oxide-oxygen for induction and maintenance of anaesthesia. *Anaesthesia.* 1987;42:360-365. 5. Cockshott ID. Propofol ("Diprivan") pharmacokinetics and metabolism: an overview. *Postgrad Med J.* 1985;61(suppl 3):45-50.

Please see last pages of this advertisement for brief summary of prescribing information.





EMULATON FOR IV ADMINISTRATION

(For full prescribing Information, see package insert.)

INDICATIONS AND USAGE: DIPRIVAN Injection is an IV anesthetic agent that can be used for both induction and/or maintenance of anesthesia as part of a behanced enesthetic technique for inpatient and outputient surgery.

DIPRIVAN injection is not recommended for obstatrics, inducting caseness section deliveries, because there are insufficient data to support its satisfy to the fetus. (See PRECAUTIONS.)

DIPRIVAN injection is not recommended for use in nursing mothers because DIPRIVAN injection has been reported to be excreted in human mittle and the effects of onal absorption of small amounts of propofol are not known. (See PRECAUTIONS.)

DIPRIVAN injection is not recommended for use in pediatric patients because safety and effectiveness have not been established. (See PRECAUTIONS.)

DIPRIVAN injection is not recommended for use at this time in patients with increased intracrantal pressure or impaired careful circuitation because DIPRIVAN injection may cause substantial decreases in mean arterial pressure, and consequently, substantial decreases in cerebral perfusion pressure. (See PRECAUTIONS.)

DIPRIVAN injection in not recommended to use at this time in patients with increased intracrantal pressure. Commended the pressure, and consequently, substantial decreases in cerebral perfusion pressure. (See PRECAUTIONS.)

DIPRIVAN injection or its components.

DIFFIVAN Injection or its components.

When general anesthesia is contraindicated or in patients with a known hypersensitivity to DIFFIVAN Injection or its components.

Warshings: DIFFIVAN Injection should be administered only by persons trained in the administration of general anesthesis. Facilities for mainteaurise of a partent airway, artificial ventilation, and oxygan eartchineat and circustatory necessitation mast be inamediately available.

DIFFIVAN injection should not be coatedly available.

DIFFIVAN injection should not be coated with blood/plasma/serum from humans and animals. The clinical significance is not known.

Striot aserptic technaliques entest always be maintained while isandling DIFFIVAN injection. The weitheld in DIFFIVAN injection is an analysis of technalique entest always to maintain and while isandling DIFFIVAN injection. The weitheld in DIFFIVAN injection is an analysis of apporting rapid growth of microorganisms. (See DOSAGE AND ADMINISTRATION), Handling Precaderes.)

PRECAUTIONS: General: A lower induction dose and a slower maintenance rate of administration should be used in eldary, debilitated and/or petiants with circulatory disorders, and those rated ASA III or IV. (See DOSAGE AND ADMINISTRATION.) Patients should be continuously monitored for early signs of significant hypotension and or bradycardia. Teatment may include increasing the rate of intrasences taid, elevation of lower dermains used or preserve agents, or administration of stropine. Agenes often occurs during induction and may persist for more than 60 seconds. Vertilatory support may be required. Because DIFRIVAN injection is an emulsion, cuution should be exercised in pelatrate with disorders of lipid metalotism such as primary hyperilipoproteinemia, alabetic hyperilipoma, and pencreatitis.

hyperliperata, and pencreatitis.

Since DPRNAN injection is never used alone, an adequate period of evaluation of the awakened patient is indicated to ensure satisfactory recovery from general anesthesis prior to discharge of the patient from the recovery room or to home.

Indicated to ensure satisfactory recovery from general anesthesia prior to discharge of the patient from the recovery room or to home.

Tensient local pain may occur during intrasenous injection, which may be reduced by prior injection of IV idiocente. Tensient local pain may occur during intrasenous injection, which may be reduced by prior injection of IV idiocente (10 mil. of a 19% solution). Venous sequelate (inhibits or thrombosis) have been reported arrayly (< 19%). In this week-controlled clinical studies using dedicated intrasenous catheters, no histanous of venous sequelate were reported up to 14 days following induction. Peth can be minimized if the larger veins of the foreign or intracultation to success of animatic caused minimal tissue recision. The artistal injection in animatis did not induce local tissue effects. One accidental intra-arterial injection has animated and other than plan, there were no major sequelates. Perforentive myocionia, narely including opisthotonus, has occurred in a temporal relationship in cases in which DPRIVAN injection has been administrated.

Rarely, a clinical syndrome witch may include bronchospasm and enythems accompanied by hypotension has occurred shortly after the administration of DPRIVAN injection unclass.

Drug interactions: As DPRIVAN injection has no vagolytic activity, premedication has usually included anticular spents (e.g., stropine or glycopyrrolate) to modify potential increases in vagal tone due to concomitant agents (e.g., succentrements of DPRIVAN injection may be reduced in patients with intranuscular or intra-enous premedication, particularly with narrotics (e.g., morphine, meperidine, and tentany) and combinations of narcotics and sedictives (e.g., benzodiazepines, barbiturates, chioral hydrats, dropertiol, etc). These agents may lore out the animal tental pressures and cardiac output.

may increase the anesthetic effects of DPFRIVAN injection and may also result in more pronounced decreases in systolic, distratic, and mean anterial pressures and cardiac output.

During maintenance of anesthesta, the rate of DPFRIVAN injection administration should be adjusted according to the desired level of anesthesta and may be reduced in the presence of supplemental analyses agents (eg., introduced or opticids). The concurrent administration of potent linelational agents (eg., isofurane, enflurane, and halothane) during maintenance with DPFRIVAN injection has not been extensively evaluated. These inhabitional agents can also be expected to increase the ensembles and cardionspariatory effects of DIPFRIVAN injection. DIPFRIVAN injection does not cause a clinically significant change in onset, intensity or duration of the commonly used neuronizacian blocking agents (eg., succipitation) and nondepotamental muscle relaxents). No significant adverse interactions with commonly used premedications or drugs used during anesthesia (including a range of muscle relaxents), inhabitional agents, analysis agents, and local anesthetic agents) have been observed.

bean observed.

Caretagements, Mutagements, Impatrment of FartiRity: Animal carcinogenicity studies have not been performed

been observed. Carefungements, Muchagaments, langariment of Pertility: Animal carcinogenicity studies have not been performed with proporol.

In vitro and in vivo animal tests tailed to show any potential for mutagenicity by proporol. Tests for mutagenicity included the Ames (using Satronnais sp) mutation test, gene mutation/gens conversion using Saccheromyces cerevisiae, in vitro cytogenetic studies in Chinese hamsters and a mouse micronucleus test. Studies in female rats at intravenous doses up to 16 mg/kg/day (8 times the madmum recommended human induction dose) for 2 weeks before pregnancy to day 7 of gestation did not show impaired fertility. Male fertility in rats was not affected in a dominant lethal study at intravenous doses up to 16 mg/kg/day for 5 days. Pragnaroy Catagary 8: Reproduction studies have been performed in rats and rabbits at intravenous doses of 15 mg/kg/day (8 times the recommended human induction dose). The nats and rabbits at intravenous doses of 15 mg/kg/day (8 times the recommended human induction dose). The performed in the net season are maternal deaths in rats and rabbits and decreased pup survival during the lactating period in durine treated with 15 mg/kg/day (6 times the recommended human induction dose). The pharmacological activity (anesthesia) of the drug on the mother is probably responsible for the adverse effects seen in the offspring. There are, however, no adequate and well-controlled studies in pregnant women. Because arimal reproduction studies are not always predictive of human responses, this drug should be used during pregnancy only if clearly needed. There are not always predictive of human responses, this drug should be used during pregnancy only if clearly needed. Including cesareen section deliveries, because there are insufficient data to support its safety to the fetus.

Marsing lighthers: DIPRIVAN injection is not recommended for use in nursing mothers because DIPRIVAN has been reported to be excreted in human milk and the effects of oral absorption of smal

not known.

Pediatric Use: DIPRIMAN injection is not recommended for use in pediatric patients because safety and

not known.

Pediatric Use: DIPRIVAN injection is not recommended for use in pediatric patients because safety and effectiveness have not been established.

Necroarungiteal Assertivesia: Studies to date indicate that DIPRIVAN injection decreases cerebral blood flow, carebral metabolic copgen consumption, and intracrantal pressure, and increases cerebrovescular resistance. DIPRIVAN injection does not seem to affect cerebrovescular reactivity to changes in arterial carbon dioddension. Despita these findings, DIPRIVAN injection is not recommended for use at this time in patients with increased intracrantal pressure or impaired carebral circulation because DIPRIVAN injection may cause substantial decreases in man arterial pressure, and consequently, substantial decreases in cerebral perfusion pressure. Further studies are needed to substantiate what happens to intracrantal pressure following DIPRIVAN injection when decreases in mean arterial and cerebral perfusion pressures are prevented by appropriate measures. ADVERSE REACTIONES: Adverse event information is derived from controlled clinical trials and worldwide marketing experience. In the description below, rates of the more common events represent US/Canadian clinical study results. Less trequent events are derived information is derived from reports of 1573 patients included in time US/Canadian clinical study results. Less trequent events are insufficient data to support an accurate estimate of their incidence rates. The following estimates of adverse events for DIPRIVAN injection are derived from reports of 1573 patients included in the US/Canadian induction and maintenance studies. These studies were conducted using a variety of premedicants, vurying lengths of surgical procedures and various other anesticete agents. Most adverse events were mild and transient.

The following adverse events were reported in patients treated with DIPRIVAN injection. They are presented within each body system in order of decreasing tregurency.

Insidesce Greater than 149—All sw

DIPPRIVANO (propotol) Injection

Hypertension. Cestral Nerveus System: Movement,* Headache, Dizziness, Twitching, Bucking/Jerking/
Threshing, Corbc/Myocknic Movement. Digastive: Nausea,** Vorniting.* Abdominal Cramping, Injection Sile:
Burning/Stinging.** Pain,** Tingling/Numbness, Coldness, Respiratory: Cough, Hiccough, Apnes (see also CLINICAL PARMACOLOGY). Sitts and Appendages: Flushing.
Incidence of unmarked events is 196-394; "3% to 1096; **10% or greater.
Isolifence Less than 19% — Cassal Relationskip Prabable (Adverse events reported only in the Sterature, not seen in clinical trials. and Naticizer).

Burning/Striging "Pain," Impling/Numbriess, Coldness, Repetations; Disting, Incidence of urmanised events is 196-394; "35% to 1095; "10% or greater, College, Least fram 194- Casseal Relationship Probable (Adverse events reported only in the literature, not seen in clinical trials, are *National*, Othest Pain, Neck Stiffness, Trunk Pain, Cardiaressectar: Biotycardia, Premature Vertificular Contractions, Premature Atrial Contractions, Syncope, Abnormal ECG, ST Segment Depression. Central Nervices System: Stiffness, Implicit, Fatigue, Maraine, Rigidity, Digastive; Hypersal-viction, Dry Mouth, Synalloving, Injection Stat: Discomfort, Philobitis, Hives/fiching, Redines/Discotoration, Abnormal Dreams, Aghtation, Corfusion, Central, Operium, Euphoria, Fatigue, Maraine, Rigidity, Digastive; Hypersal-viction, Dry Mouth, Synalloving, Injection Stat: Discomfort, Philobitis, Hives/fiching, Redines/Discotoration, Massaciates/abetative, Number of State (State of State Online), Personal Redines/State (State Online), Personal Redines/S

Inthi-Bouorisms) supposition assess that it is a suppose a group of the profile.

Influsion rates should always be titrated downward in the absence of clinical signs of light anesthesia until a mild response to surgical stimulation is obtained in order to avoid administration of DVPRVAN injection at rates higher than are clinically necessary. Generally, rates of 0.05 to 0.1 mg/kg/min should be achieved during maintenance.

than are clinically necessary. Generally, races of ULD to U.T. my nyman should be exhibited unit optimize recovery times.

Indirection 25 mg (2.5 mL) or 50 mg (5.0 mL) may be administered with nitrous code in patients undergoing general surgery. The incremental botises should be administered when changes in vital signs indicate a response to surgical stimulation or light anesthesia, such as stropine, DIPRIVAN injection has been used with a variety of agents commonly used in aneathesia, such as stropine, scoppolamine, glycopyrrolata, diszepam, depotenting and nondepoterzing muscle relevants, and nanotic analogosics, as well as with inhalational and regional aneathetic agents. (See Drug Interactions.)

DORAGE DIRECT

DOSNOC GUIDE			
INDICATION	DOSAGE AND ADMINISTRATION		
Induction	Dosage should be individualized. Askilla: Are likely to require 2.0 to 2.5 mg/kg (approximately 40 mg every 10 seconds until induction onset). Eliferty, Debilitated, hypovolema's and/or ASA Mil or IV Patients: Are likely to require 1.0 to 1.5 mg/kg (approximately 20 mg every 10 seconds until induction onset).		
Majytaquace Influsion Intermittent Bolus	Variable rate infested — thrated to the desired clinical effect. Adults: Generally, 0.1 to 0.2 mg/kg/min (6 to 12 mg/kg/h). Elderly, Debilitating, Hypovedsmic and/or ASA Ni or IV Patiests: Generally, 0.05 to 0.1 mg/kg/min (3 to 6 mg/kg/h). Increments of 25 mg to 50 mg, as needed.		

Competibility and Stability: DIPRIVAN Injection should not be mixed with other therapeutic agents prior to

Compatibility and Shibility: DIPRIVAN Injection should not be mixed with other therapeutic agents prior to administration. Illustrate Prior to Administration. It should only be diluted with 5% Dectroes injection, USP, and it should not be diluted prior to administration, it should only be diluted with 5% Dectroes injection, USP, and it should not be diluted to a concentration less than 2 mg/mL because it is an emulsion. In diluted form it has been shown to be core stable when in contact with glass than with plastic (95% potency after 2 hours of running infusion in plastic.)

Administration lots a Running IV Catheter: Compatibility of DIPRIVAN Injection with the contact with plastic compatible with the following intravenous fluids when administrated into a running IV catheter.

—5% Dectroes an Injection, USP
—Lactated Ringers injection, USP
—Lactated Ringers injection, USP
—5% Dectroes and 0.25% Sodium Chloride injection, USP
—5% Dectroes and 0.25% Sodium Chloride injection, USP
Handling Procedures: Perenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and combiner permit.

Do not use if there is evidence of separation of the phases of the emulsion.

Strict aseptic techniques must always be maintained during handling as DIPRIVAN Injection is a single-use parenteral product and contains no artificatoidal preservatives. The vehicle is capable of supporting rapid growth of microorganisms.

of microorganisms.

DPRIVAN injection should be drawn into startle syringes immediately after ampules are opened. Administration should then commence without extended delay.

DIPRIVAN injection should be prepared for single patient use only and any unused portions of DIPRIVAN injection or solutions containing DIPRIVAN injection must be discurded at the end of the surgical procedure. Failure to follow assiptic handling procedures may result in microbial contamination causing leverandor other adverse consequences which could lead to life-threatening tilness.

Made in Sweden

Manufactured for:



STUART PHARMACEUTICALS A business unit of ICI Americas Inc. Wilmington, Delaware 19897 USA

Classified Advertising

The Department of Anesthesiology of St. Louis University School of Medicine is seeking board-qualified or certified fulltime faculty to fill newly created positions to meet the needs of the expanding residency program and new expanding hospital facility. Training and interests in the subspecialty areas of pediatrics, cardiovascular, and neuroanesthesia are desirable. These clinical/teacher positions will also promote academic interests and research development. Participation in the residency training program is essential. The university is committed to affirmative action. Inquiries should be directed to John F. Schweiss, MD, Chairman, Department of Anesthesiology, St. Louis University School of Medicine, 3635 Vista Avenue at Grand Boulevard, St. Louis, MO 63110-0250; telephone (314) 577-8750.

544L/E

MAINE

BC or BE MD to join group of three MD anesthesiologists and four CRNAs in the practice of anesthesia, intensive care, and respiratory care. Phone (207) 622-1959 from 8:30 AM to 3:30 PM. Write to Chief of Anesthesia, Kennebec Valley Medical Center, 6 East Chestnut Street, Augusta, ME 04330.

OHIO

Anesthesiologist, University Hospitals. Must be at least board eligible. Equal Opportunity, Affirmative Action Employer. Send curriculum vitae to Helmut F. Cascorbi, MD, PhD, Professor and Chairman, Department of Anesthesiology, University Hospitals of Cleveland, 2074 Abington Road, Cleveland, OH 44106.

571A/F

ILLINOIS, CHICAGO

Anesthesiologist BC/BE to join expanding group practice limited to outpatient anesthesia. Excellent opportunity for growth. Send CV to Marc Sloan, MD, 25 East Washington, Suite 300, Chicago, IL 60602

574A/F

The UCLA Department of Anesthesiology has openings for faculty with experience in anesthesia for organ transplantation. Requisites include clinical and teaching skills; eligibility for a California medical license; ABA certification or in process. Address correspondence with names of five references and curriculum vitae to Stuart F. Sullivan, MD, Department of Anesthesiology, UCLA School of Medicine, Los Angeles, CA 90024-1778. UCLA is an Affirmative Action, Equal Opportunity Employer.

584A/F

THE UNIVERSITY OF NEW MEXICO

A reorganized, expanding Department of Anesthesiology in the "Land of Enchantment" has seven immediate openings at the assistant and associate professor levels. Responsibilities include teaching of medical students and residents and the provision of clinical care in a busy tertiary referral center. Opportunities to pursue research interest will be provided. Experience in cardiac, obstetric, neurosurgical, and pediatric anesthesia is desirable. Qualified candidates should address inquiries to James C. Scott, MD, Associate Professor and Acting Chairman, Department of Anesthesiology, University of New Mexico School of Medicine, 2211 Lomas NE, Albuquerque, NM 87106; (505) 843-2610. The University of New Mexico is an Equal Opportunity, Affirmative Action Employer.

585A/F

Cardiac anesthesiologists and Director of Obstetric Anesthesiology sought for academic medical center practice. Candidates for obstetric position must have experience in all types of obstetric anesthesia. Interest in research and teaching highly desirable. Present staff of 25 MDs, over 40 CRNAs, and over 20 residents provides challenging anesthesia care team setting. OR area contains state-of-the-art equipment in 20 new or renovated suites. Interested applicants should send CV and three references to Dr. Philip Lumb, Professor and Chairman, Albany Medical College, Department of Anesthesiology, Code A-131, Albany, NY 12208. EOE.

592B/F

Anesthesiologist BC/BE to work with four MDs in 200+ bed hospital and surgicenter midway between Milwaukee and Chicago. Fee for service. Send CV and references to Dr. I. Romana, PO Box 594, Kenosha, WI 53141.

597B/E

FLORIDA

Central Florida Area—Excellent opportunity for MD with fellowship or extensive clinical experience in chronic pain management. Salary to partnership. Reply Box 613C/E.

613C/E

BE/BC ANESTHESIOLOGIST

SW PA, 300-bed, modern community hospital to work with 3 MDs and CRNAs. Competitive starting salary with malpractice and BC/BS. No open heart, minimal OB, minimal neuro. Reply to Box 614C/F.

BC/BE anesthesiologist for expanding ambulatory group practice. Part time/full time with no nights, emergencies, OB, or weekends. Please reply to Box 621C/H.

621C/H

CLASSIFIED ADS

Anesthesia and Analgesia makes available classified advertising space for those interested in obtaining positions or wishing to announcements, postgraduate courses, or other pertinent events. We require that all advertisements be relevant to the practice of anesthesia and analgesia, and we reserve the right to refuse adver-tisements that are not relevant.

Specifications. Ads should be typewritten on Specifications. Ads should be typewritten on letterhead stationery; the text should be double-spaced, with the title or key phrase typed in capital letters. Enclose two photocopies with each ad. Display space (minimum ¹/₄ page) is available through Pharmaceutical Media, Inc., 440 Park Avenue South, 14th floor, New York, NY 10016, telephone: (212) 685-510, FAX: (212) 685-6106. 685-6126.

Rates. Ads cost \$1.25 per word per insertion, with a minimum of 20 words. Abbreviations, dates, initials, post office box numbers, telephone numbers, vears, and zip codes are considered one word each. There is an additional

fee of \$17.00 per insertion for box number ads.*

Payment. Full payment or institutional purchase order must accompany the copy for each ad. Ads received without a check or purchase order will be returned. (Make checks payable to

order will be returned. (Make checks payable to Elsevier Science Publishing Company, Inc.)

Deadline. Copy must be received 7 weeks before publication date (i.e., by January 1 for the March issue); multiple-insertion ads are welcome. Ads may run up to 6 months per purchase order/payment. Please specify in which issue(s) your advertisement is to appear.

Send all ad copy, payments, and correspondence to: Anesthesia and Analgesia Classified Ads, Desk Editorial, Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010.

NY 10010.
*When responding to a box number ad, include the box number on all correspondence.

PENNSYLVANIA

Immediate opening for BC/BE anesthesiologist to join 2 MDs and CRNAs in PA. Fee for service. Call Dr. Shah, (717) 242-7186, 9 AM to 5 PM.

623CDF

ILLINOIS

Anesthesiologist to join congenial group of MDs/CRNAs expanding to provide anesthesia coverage for only hospital in city since recent merger. No open heart or neurosurgery. Environment conducive to family living, variety of schools, recreation. Good opportunity with stable future. City located in east central Illinois with population of approx. 40,000 (35 mile radius service area with 126,126 population). Within driving distance of Chicago and Indianapolis. Please send CV to Box 624C/H.

624C/H

ALABAMA-ANESTHESIOLOGIST

Faculty position for clinical BC/BE anesthesiologist at University of Alabama at Birmingham, Department of Anesthesiology. Opportunities to do clinical research, variety of clinical cases including liver transplantation. Desire to participate in teaching necessary. Limited night call. Generous benefit package. Salary competitive with private practice situations. Located in downtown Birmingham; city rated "America's most livable city" by U.S. Conference of Mayors, June 1989, and rated by Newsweek, February 1989, as "one of the nation's top 10 hot cities." Please contact Simon Gelman, MD, PhD, Professor and Chairman, Department of Anesthesiology, University of Alabama at Birmingham, 619 South 19th Street, Birmingham, AL 35233, (205)934-4696. An Affirmative Action/Equal Employment Opportunity Employer.

626C/F

DIRECTOR, PAIN MANAGEMENT SERVICE The Department of Anesthesiology at the Oregon Health Sciences University is recruiting for a Director of our Pain Management Service. The Service encompasses management of acute and chronic pain, training of medical students, residents, and fellows, and research. The Service provides a multidisciplinary approach to pain control and has vigorous clinical psychology and neuroimplant components. Excellent interdisciplinary relationships exist with neurosurgery, orthopedics, and surgical oncology. Board eligibility in anesthesiology or equivalent certification plus training and/or experience in pain management are required. Research experience and evidence of productivity are desired. Academic rank for successful candidate will be determined by qualifications. Candidate must be eligible for Oregon medical license.

Please send curriculum vitae and names of three references to Wendell C. Stevens, MD, Department of Anesthesiology, OHSU, 3181 SW Sam Jackson Park Road, Portland, OR 97201. The Oregon Health Sciences University is an Equal Opportunity/Affirmative Action Employer.

627C/E

FULL-TIME ANESTHESIOLOGIST

BC or BE to join a group of anesthesiologists and CRNAs providing all types anesthesia coverage, though little obstetrical, to three hospitals and a day surgery facility in a southwest Louisiana city of approximately 75,000. Please send CV to Lake Charles Anesthesiology, 1415 18th Street, Lake Charles, LA 70601.

634C/H

ANESTHESIOLOGY CA-4 CRITICAL CARE MEDICINE

CA-4 training in Critical Care Medicine satisfying the requirement for certification of specialty competence in critical care medicine through anesthesiology. Newly approved program at the Albany Medical Center. Two positions available for July 1991. Send CV to Carol Kiner, Albany Medical Center, Anesthesia A-131, Albany, NY 12208

631D/C

ANESTHESIOLOGIST

Board certified/eligible to join expanding small group practice. Experienced in all anesthesia techniques including epidural block and pain management. No open heart or neurosurgery. Good opportunity for growth. Please send CV to Mount Vernon Anesthesia Associates, Box 391, Mount Vernon, OH 43050.

633D/F

NORTHERN NEW ENGLAND

Chief and/or Staff Anesthesiologist, BC/BE for 194-bed VA Medical Center, fully affiliated with Dartmouth-Hitchcock Medical Center and Dartmouth Medical School. Active teaching hospital. Academic appointment and salary commensurate with experience. Part-time position a possibility. Good schools, cultural offerings, beautiful country environment, good skiing, excellent book store. Two and a half hours from Boston, Massachusetts—one and a half hours from Burlington, Vermont. For further information, call John M. Head, MD, Chief of Surgery, or Susanne Learmonth, Acting Chief of Anesthesia, (802) 295-9363, extension 5290, or FTS 834-1290, or send CV to above at VA Medical Center, White River Junction, VT 05001. EOE/MF.

635D/F

PEDIATRIC ANESTHESIA

Due to expansion of our clinical responsibilities, positions are available for pediatric anesthesiologists at Arkansas Children's Hospital. We provide primary and tertiary care for children locally and in six surrounding states. We are especially interested in those with special training or experience in pediatric cardiovascular anesthesia and pain management. Please send replies to Raeford E. Brown, Jr., MD, Chief, Division of Pediatric Anesthesia, Arkansas Children's Hospital, 800 Marshall Street, Little Rock, AR 72202-3591. An Equal Opportunity Employer.

636D/F

STAFF MDA

Need ASAP or 7/91. Midwest Metro, 399 beds, BE/BC. Includes heart-OB-pain. Relaxed, excellent work/living environment. Send CV to A.M.I., P.O. Box 2153, Shawnee Mission, KS 66201.

640D/F

MOUNTAIN SOUTHWEST

Anesthesia care team in level II trauma center seeks anesthesiologists and CRNAs for full-time and part-time positions. Reply in confidence to Box 642D/F.

642D/F

MAINE

Anesthesiologist needed to join five-anesthesiologists, 10-CRNA group doing wide range of surgeries at two community hospitals. No open heart. Picturesque central Maine location near lakes, mountains, and ocean. Referral area of 75,000+. Competitive compensation package. Contact Jill Gilbert at (207) 872-1136 or send CV to Waterville Anesthesia Associates, 44 Main Street, Waterville, ME 04901.

643D/G

MICHIGAN

Expanding surgery load results in opening of attractive permanent position for BC/BE "Team Player" in four-person fee-for-service practice in friendly four-season recreational, lakeside community. Share call and 3800 cases annually at 174-bed hospital. Little OB, no OH or neuro. Send inquiries and CV to Stephanie Riemer, Mercy Hospital, 400 Hobart Street, Cadillac, MI 49601, or call (616) 779-7404.

645D/F

ANESTHESIOLOGIST

Department of Anesthesiology at the SUNY Health Science Center in Syracuse, N.Y. is recruiting faculty at the instructor and assistant and associate professor levels. Qualified individuals with a strong academic commitment in all types of anesthesia, critical care, and pain management are sought. SUNY Health Science Center is a tertiary care center and provides clinical

services also to the Syracuse Veterans Administration Hospital. Rank and salary are commensurate with experience. Must be board certified or board eligible and possess a New York State medical license. Please send letter, curriculum vitae, names, addresses, and phone numbers of three references to Enrico M. Camporesi, MD, Professor and Chairman, Department of Anesthesiology, SUNY Health Science Center, Syracuse, NY 13210. The State University of New York Health Science Center is an Equal Opportunity/AA Employer.

652D/F

Anesthesiologist with experience and expertise in acute and chronic pain management is sought to establish a pain management service for both inpatients and outpatients. Ours is a large group practice in the mountains of the southeastern U.S. Compensation and benefits will be commensurate with training, experience, and board certification. Reply to Box 653D/G.

CALIFORNIAThe UCLA Department of Anesthesiology is searching for a faculty person with experience in ophthalmologic anesthesia to be Chief of the Ophthalmologic Anesthesia Division. Candidates are required to show evidence or promise of research productivity and scholarly writing. Other requisites include clinical and teaching skills, commitment to discovery, eligibility for a California medical license, ABA certification. Address correspondence with names of five references and curriculum vitae to Thomas M. Grove, MD, PhD, Department of Anesthesiology, UCLA School of Medicine, Los Angeles, CA 90024-1778. UCLA is an Affirmative Action, Equal Opportunity Employer.

654D/F

PAIN MANAGEMENT

Excellent position for BE/BC anesthesiologist with pain management fellowship or experience. Excellent pay, no call, no weekends, 7-5 job, OR coverage available. Wonderful "cajun city," close to New Orleans and Houston. Early partnership. Great financial potential. 1-318-468-4016.

656DE

UNIVERSITY OF PENNSYLVANIA

Anesthesiology Research Training: Applications are invited for 2 years full time in an NIH funded, Training for Anesthesia Research program. The specific program (and areas of training) is individually designed to meet the needs of each trainee and is usually a mix of course work and laboratory or clinical research activities. The research training is coordinated between the Department of Anesthesia and the chosen basic

science field. For information write (include current CV) to Bryan E. Marshall, MD, FRCP, Director, Training for Anesthesia Research Program, 781 Dulles, Department of Anesthesia, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104.

657D/F

FULL-TIME ANESTHESIOLOGIST

To join a five-man group in northern Rockies for general practice of anesthesiology except cardiac. Small city environment with good local services and schools. Access to multiple airlines. Ready access to recreational activities. Reply to Box 658E.

658E

MUSKEGON, MICHIGAN

Private anesthesia group seeking anesthesiologists to join a seven-man group of physicians employing five CRNAs. We practice in two hospitals with a total capacity of 600–700 beds. All specialty modalities represented. If interested, please write to Frederick Wakerley, DO, or Carsten Boysen, MD, 1060 West Norton Avenue, Muskegon, MI 49441.

659E/G

OHIO

BC/BE, to join growing group of anesthesiologists and CRNAs at 475-bed, universityaffiliated hospital on Ohio's North Coast. All types of surgery except organ transplantation. Send CV to North Coast Anesthesiologists, 11311 Shaker Boulevard, Cleveland, OH 44104.

660E/G

CALIFORNIA

Anesthesiologist needed for Palm Springs group practice. Resort community. All types of anesthesia except heart and trauma. Excellent compensation package leading to partnership. Please send CV to Director of Anesthesiology, 73-925 Highway 111, #L, Palm Desert, CA 92260.

661E

MISSISSIPPI: ANESTHESIOLOGY FACULTY, UNIVERSITY OF MISSISSIPPI MEDICAL CENTER

Major reorganization and expansion of academic department under new chairman creates opportunities at all levels, instructor to professor, for generalists and for subspecialists with training and/or experience in pediatric, obstetric, cardiac, neuro, and ambulatory anesthesia, intensive care, and pain management (acute and chronic). Active clinical and didactic resident teaching required. Clinical and laboratory research possible and encouraged; space and start-up funds available. A wealth of inter-

esting and challenging clinical cases comes from statewide referrals. Also need for a clinical director with some administrative (OR/schedule/personnel) experience. All positions require eligibility for Mississippi licensure. ABA certified or examination process. Rank and academic salary determined by qualifications. Generous practice compensation. Remarkably pleasant and affordable living in Jackson, the urban "Bold New City" of the South, a state capital with a metropolitan area population of over 400,000, outstanding schools, culture, and recreation/outdoor activities. Please forward inquiry and CV to John H. Eichhorn, MD, Professor and Chairman, Department of Anesthesiology, The University of Mississippi Medical Center, 2500 North State Street, Jackson, MS 39216-4505. An equal opportunity employer, M/F/H/V.

CHAIR: DEPARTMENT OF ANESTHESIOL-OGY, THE UNIVERSITY OF TEXAS MEDICAL **BRANCH AT GALVESTON**

Applications and nominations are invited for the position of Chair of the Department of Anesthesiology. Candidates must be highly qualified with nationally recognized credentials in research and senior academic accomplishments with administrative experience or potential. The position offers excellent opportunity to develop an internationally leading academic department with outstanding resources, scientific environment, and faculty positions.

Application or nomination should include a curriculum vitae. Address correspondence to Courtney M. Townsend, Ir, MD, Robertson-Poth Professor, Department of Surgery, The University of Texas Medical Branch, Galveston, TX 77550. The University of Texas Medical Branch is an Affirmative Action/Equal Opportunity Employer.

663EF

BC/BE anesthesiologist for a 500-bed tertiary hospital in a Florida coastal city. Immediate opening. Liberal salary and early partnership. Send resume to Box 664EF.

664EF

ADIRONDACK—LAKE CHAMPLAIN RE-

Upstate New York-growing, active department seeks additional BC/BE anesthesiologist. Limited OB, neuro, and pediatrics; no open heart. Excellent starting salary. Close to Montreal and the Olympic-Lake Placid region. If you enjoy skiing and sailing, contact us for more details: Hannah Hanford, P.O. Box 1656, Plattsburgh, NY 12901; (518) 643-2998.

OHIO STATE UNIVERSITY, COLUMBUS

The Department of Anesthesiology, due to program expansion, is recruiting for CA-3

(PGY IV) housestaff positions for July 1, 1991 through June 30, 1992. OSU is a 1000bed regional referral, Level I Trauma and Burn Center. Rotations are available in obstetric anesthesia, advanced clinical track, pediatric anesthesia, SICU/critical care, and research. For further information contact Residency/Education Coordinator, Department of Anesthesiology, The Ohio State University Hospitals, N-429 Doan Hall, 410 West Tenth Avenue, Columbus, OH 43210.

FELLOWSHIP—PEDIATRIC CARDIAC ANES-

Applications are being accepted for a 12month academic fellowship (CA-4) starting in July 1991 and thereafter. Clinical training on dedicated service with 1000 cardiac OR and 400 Cath Lab cases per year. Research training for up to 6 months included. Address correspondence with CV to Paul R. Hickey, MD, Cardiac Anesthesia Service, Children's Hospital, 300 Longwood Avenue, Boston, MA 02115.

667EGIKAC

OHIO STATE UNIVERSITY, COLUMBUS
The Department of Anesthesiology is re-

cruiting board certified/eligible anesthesiologists with interest, training, and experience in all aspects of regional anesthesia. The applicant will be responsible for resident and medical student teaching, research, and patient care as division director of this important area. We are an Affirmative Action/Equal Opportunity Employer. Please send CV to J.S. McDonald, MD, Professor and Chairman, Ohio State University Hospitals, Department of Anesthesiology, 410 West Tenth Avenue, Columbus, OH 43210.

ANESTHESIOLOGIST BC/BE
To join one-MD, three-CRNA group. Northwestern Pennsylvania community hospital. Minimal OB, no neuro or cardiac. Easy call schedule. Family-oriented community; hunting, fishing, skiing in area. Competitive salary and benefits leading to partnership. Send CV to Box 669E.

669E

The University of New Mexico Department of Anesthesiology is recruiting a VA Chief of Service for its department at the New Mexico Regional Medical Facility (VA Hospital) in Albuquerque. Requirements include proven administrative, teaching, and leadership abilities, academic experience, and board certification. Appointment will be at the associate or full professor level. Qualified candidates should contact Jorge Estrin, MD, PhD, Chairman, Department of Anesthesiology, University of New Mexico School of Medicine, 2211 Lomas

Boulevard, N.E., Albuquerque, NM 87106; (505) 843-2610. The University of New Mexico is an Equal Opportunity, Affirmative Action Employer.

The University of New Mexico Department of Anesthesiology is recruiting faculty for the following: (1) Obstetrical Anesthesia at the assistant, associate, or full professor rank. (2) Critical Care Medicine at the assistant or associate level. It is expected that candidates for CCM positions will have or be eligible for subspecialty certification. Faculty responsibilities include provision of clinical care, teaching, and research. Qualified candidates should send a CV or contact Jorge Estrin, MD, PhD, Chairman, Department of Anesthesiology, University of New Mexico School of Medicine, 2211 Lomas Boulevard, N.E., Albuquerque, NM 87106; (505) 843-2610. The University of New Mexico is an Equal Opportunity, Affirmative Action Employer.

CARDIOVASCULAR FELLOWSHIP OPPOR-

The Department of Anesthesiology at the University of New Mexico School of Medicine has openings at the CA-4 level for advanced training in cardiovascular anesthesiology. The fellowship is a 2-year, comprehensive program designed to train the fellow for a career in cardiovascular anesthesiology. Research in cardiovascular physiology and anesthesia, provision of clinical care for complex adult and pediatric cases, participation in conferences, and teaching responsibilities are part of the fellowship experience. Interested individuals should contact Jorge Estrin, MD, PhD, Professor and Chairman, Department of Anesthesiology, University of New Mexico, 2211 Lomas Boulevard, N.E., Albuquerque, NM 87106; (505) 843-2610. The University of New Mexico is an Equal Opportunity, Affirmative Action Employer.

672EF

PAIN MANAGEMENT TRAINING AND PRACTICE

Looking for physicians interested in pain management. Graduates of pain fellowships and anesthesiology residencies are encouraged to apply. Will also consider and train physicians from other specialties who are interested in changing directions and going into the professionally and financially rewarding practice of pain management.

Training will be done in a busy, private practice, intervention-oriented pain management center, located in Dallas, Texas. The center emphasizes a wide variety of pain-relieving procedures with management of psychological and physical rehabilitation aspects in the patient's care. Attention will also be given to development of administrative knowledge in the management of a private pain practice. After training, physicians may be able to join our staff, or get our help and support in developing their own challenging and potentially lucrative pain management practices.

Training period may vary from 3 months to 1 year depending on previous training. Compensation during training is highly competitive and after training it is, potentially, outstanding. Texas license is required.

Please send CV to P.O. Box 802314, Dallas, TX 75380-2314, or call (214) 239-2190 for more information.

673E

CA-III AND CA-IV POSITION IN PEDIATRIC ANESTHESIOLOGY

The Department of Anesthesia at New England Medical Center Hospitals, Boston Floating Hospital, Boston, Massachusetts (Tufts University) is accepting applications for a CA-III and/or CA-IV position in pediatric anesthesia. This is a 6-month to 1-year experience specializing in all aspects of pediatric anesthesia. The position is available beginning July 1991. Please include CV with letter to W. Heinrich Wurm, MD, Acting Chairman, Department of Anesthesia, Box 298, 750 Washington Street, Boston, MA 02111.

POSTDOCTORAL FELLOWSHIP

Background in clinical medicine or clinical research required for studies with patients with heart disease undergoing surgery. Cardiac function and ischemia assessed with ECG, Holter, and echocardiography monitoring. Working with cardiologists, epidemiologists, and anesthesiologists. Send CV and names of three references to Dennis T. Mangano, PhD, MD, Professor and Vice Chairman, Department of Anesthesia, University of California, San Francisco, 4150 Clement Street (129), San Francisco, CA 94121.

674E/D

ACADEMIC CRITICAL CARE PEDIATRICIAN Children's Hospital Medical Center, Cincinnati, Ohlo, a 350-bed University-affiliated teaching hospital, is seeking a fulltime director of pediatric critical care. Candidates should be eligible for academic appointment at the associate professor or professor level at the College of Medicine at the University of Cincinnati. Applicants must be board certified or board eligible in pediatric critical care medicine or possess equivalent qualifications. Responsibilities include direction of the clinical program which has 27 beds and includes a cardiac care unit, a general unit, and isolation facilities; and direction of a pediatric critical care fellowship program. It is anticipated that the successful candidate will have demonstrated productivity in clinical or basic research. Forward applications to Robert W. Wilmott, MD, Chairman, ICU Search Committee, Children's Hospital Medical Center, Elland and Bethesda Avenues, Cincinnati, OH 45229-2899. Children's Hospital Medical Center is an Equal Opportunity, Affirmative Action Employer.

676E

SITUATION WANTED

U.S. born—U.S. trained—board certified in pain management. Will complete Pain Management Fellowship in July 1991. Desires anesthesia practice with strong emphasis on pain management. Prefer West Coast. Will consider western United States. Age 42. Twelve years private practice experience. Call (913) 681-8543 evenings only (central time zone), or reply to box 677EF.

677E

GEORGIA: The Medical College of Georgia Two faculty positions are open in the Department of Anesthesiology, one position with privileges based at the Veterans Administration Medical Center. BC/BE anesthesiologists qualified to obtain Georgia licensure. Interest in resident education and the desire to participate in all aspects of practice. AA/EEO Employer. Please submit CV to Mrs. Susan Guillebeau, Secretary to Chairman, Anesthesiology, BIW-227, Medical College of Georgia, Augusta, GA 30912-2700.

678E

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July opening for a BC/BE anesthesiologist to join a large private practice group. Excellent salary and benefits, including medical/dental, disability and life, professional dues and insurance, generous meeting allowance, relocation expense, profit-sharing, pension plan, and early partnership. Send CV and cover letter to Box 679E.

679E

FELLOWSHIP AND CA3: Positions in Pain Management

The Pain Management Center at The Cleveland Clinic Foundation has positions available for those interested in advanced training in acute and chronic pain management. A large multidisciplinary program for inpatents and outpatients provides care for a wide range of chronic pain states. The Pain Center is integrated with the Spine Center, a well-established Drug Dependency Unit in the Department of Psychiatry, and the Cancer Center, and fellows are encouraged to spend a varying amount of their training in these three areas. Fellows will gain experience in the medical management of chronic and acute pain patients, and, in addition, will be involved with regional

anesthetic techniques and neurologic procedures. As the chronic patient population contains a large number of patients suf-fering from sympathetically maintained pain states, experience will also be gained in the medical management and techniques used in these patients. Fellows are expected to participate and CA-3 residents will be given the opportunity to undertake research on the acute and chronic pain services. Twelve-month fellowships are available for residents having successfully completed a CA-3 year, as are CA-3 programs of 6 or 12 months. Inquiries may be directed to Michael Stanton-Hicks, MB, BS, MD, Director, Pain Management Center, Department of General Anesthesiology, The Cleveland Clinic Foundation, 9500 Euclid Avenue, M-60, Cleveland, OH 44195-5254; telephone (216) 444-3769.

680E

ANESTHESIOLOGIST

BC/BE to participate in teaching/research program affiliated with University of Iowa College of Medicine. Duties include supervising third- and fourth-year residents. Prior teaching experience desirable. Salary dependent upon qualifications. Send resume or application to Lester Dragstedt, MD, Chief, Surgical Service, VA Medical Center, 30th and Euclid, Des Moines, IA 50310. EOE.

6811

CALIFORNIA ANESTHESIOLOGIST(S)

The Department of Anesthesia, University of California, San Francisco, seeks candidates at the assistant or associate level(s) for teaching and clinical responsibilities at the Veterans Administration Hospital in San Francisco. Candidates must have training in clinical cardiovascular research. The ongoing research studies are multidisciplinary and multicenter, addressing perioperative ischemia and morbidity. The University of California is an Equal Opportunity Affirmative Action Employer. Please forward curriculum vitae and three references to Ronald D. Miller, MD, Professor and Chairman, or, Dennis Mangano, MD, PhD, Professor, Department of Anesthesia, UCSF, 521 Parnassus Avenue, Box 0648, Room C-455, San Francisco, CA 94143-

682EF

PAIN MANAGEMENT FELLOWSHIP

The Pain Consortium of Greater Kansas City is offering a 12-month fellowship in pain management. This is a unique training opportunity for a highly motivated, patient-oriented anesthesiologist to participate in a strong clinical pain management program. Emphasis is on comprehensive evaluation and the use of neural blockade in the treatment of acute, chronic, and cancer pain. Training in interventional pain

management techniques including implantable drug delivery systems and CT-guided neurodestructive procedures is integrated with strong individual clinical teaching.

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683E/G

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For surgical procedures 90 minutes or longer...

ARDUAN (pipecuronium bromide for injection

Long-acting muscle relaxation without vagolytic effects¹

- Does not cause elevation of heart rate or blood pressure.²
- Recommended when cardiovascular stability is desired.³
- A useful alternative to pancuronium in patients where tachycardia is best avoided.⁴
- Provides good to excellent intubating conditions within 2.5 to 3.0 minutes.

See following page for brief summary of prescribing information.



ARDUAN (pipecuronium bromide)

Before prescribing, please consult complete product information, a summary of which follows:

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

CONTRAINDICATIONS: None known

WARNINGS: ARDUAN® (PIPECURONIUM BROMIDE) FOR INJECTION SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH THE DRUG'S ACTIONS AND THE POSSIBLE COMPLICATIONS OF ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND AN ANTAGONIST ARE WITHIN IMMEDIATE REACH. IT IS RECOMMENDED THAT CLINICALISMS ADMINISTERING COME. CIANS ADMINISTERING LONG-ACTING NEUROMUSCULAR BLOCKING AGENTS SUCH AS ARDUAN® EMPLOY A PERIPHERAL NERVE STIMULATOR TO MONITOR DRUG response, need for additional relaxant, and adequacy of spontaneous RECOVERY NEED FOR ADDITIONAL RELAXANT, AND ADEQUACT OF SPONIANEOU.

RECOVERY OR ANTAGONISM. In patients with myasthenia gravis or myasthenic (Eaton-Lambert) syndrome, small doses of non-depolarizing neuromuscular blocking agents may have profound effects. Shorter-acting muscle relaxants than ARDUAN® may be more

PRECAUTIONS: General: Since ARDUAN® has little or no effect on the heart rate, the drug will not counteract the bradycardia produced by many opioid anesthetic agents or vagal stimulation. Consequently, bradycardia during anesthesia may be more common with ARDUAN® than when a muscle relaxant (such as pancuronium) which exerts vagolytic action

Renal Failure: ARDUAN*, in the dose of 70 µg/kg actual body weight (ABW), has been studied in a limited number of patients (n=20) undergoing renal transplant surgery recently dialyzed in preparation for cadaver renal transplant. The mean clinical duration (injection to 25% recovery) of 103 minutes was not judged prolonged; however, there was wide individual variation (30 to 267 minutes). ARDUAN* has not otherwise been studied in patients with renal failure (for elective or emergency non-renal surgery). Because it is primarily excreted by the kidney, and because some shorter-acting drugs (vecuronium and atracurium) have a more predictable duration of action in patients with renal dysfunction, ARDUAN* should be used with extra caution in patients with renal failure.

Increased Volume of Distribution: Conditions associated with an increased volume of distribution, eg, slower circulation time in cardiovascular disease, old age, or edematous states, may be associated with a delay in onset time. Because higher doses of ARDUAN® may produce a longer duration of action, the initial dose should not usually be increased in these patients to enhance onset time; instead, more time should be allowed for the drug to e maximum effect

Hepatic Disease: There are no data on dosage requirements, onset, duration, or pharmacokinetics in patients with moderate or severe hepatic dysfunction and/or biliary obstruc-tion. This should be considered in selection of muscle relaxants for use in these patients.

Obesity: The most common patient condition associated with prolonged clinical duration was obesity, defined as 30% or more over ideal body weight (IBW). Clinical study subjects were dosed on the basis of actual body weight, which may have contributed to the higher incidence of prolonged duration. It is therefore recommended that dosage be based upon ideal body weight for height in obese patients.

Malignant Hyperthermia (MH): Human malignant hyperthermia has not been reported with the administration of ARDUAN®. Because ARDUAN® is never used alone and reported with the administration of AKDUAN*. Because AKDUAN* is never used alone and because the occurrence of malignant hyperthermia during a nesthesia is possible even in the absence of known triggering agents, clinicians should be familiar with early signs, confirmatory diagnosis, and treatment of malignant hyperthermia prior to the start of any anesthetic. In an animal study in MH-susceptible swine (n=7), the administration of ARDUAN* was not associated with the development of malignant hyperthermia.

Central Nervous System: ARDUAN* has no known effect on consciousness, the pain threshold, or cerebration. Therefore, administration must be accompanied by adequate

Drug Interactions: ARDUAN® can be administered following recovery from succinylcho-

line when the latter is used to facilitate endotracheal intubation.

The use of ARDUAN® before succinylcholine, in order to attenuate some of the side effects of succinylcholine, is not recommended because it has not been studied.

There are no clinical data on concomitant use of ARDUAN® and other non-depolarizing

Inhalational Anesthetics: Use of volatile inhalation anesthetics has been shown to enhance the activity of other neuromuscular blocking agents on the order of enflurane > isoflurane > halothane. No definite interaction between ARDUAN® and halothane, as used clinically, has been demonstrated. Use of isoflurane in one study of 25 patients resulted in an increase in mean clinical duration by 12%. In another study of 25 patients resulted in a increase in mean clinical duration by 12% in another study of 25 patients first anesthetized with enflurane for 5 minutes or more, the mean clinical duration was increased by 50%. Therefore, a prolonged clinical duration following initial or maintenance doses and prolonged recovery from neuromuscular blocking effect of ARDUAN* should generally be anticipated with enflurane > isoflurane > halothane.

Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentomicin, and dihydrostreptomycin); tetracyclines; bacitracin; administration of the production polymyxin B; colistin; and sodium colistimethate

Other: Experience concerning injection of quinidine during recovery from use of other mus-cle relaxants suggests that recurrent paralysis may occur. This possibility must also be considered for ARDUAN* ARDUAN* induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). In addition, experience with other drugs has suggested that acute (eg, diarrhea) or chronic (eg, adrenocortical insufficiency) electrolyte imbalance may alter neuromuscular blockade. Since electrolyte imbalance and acid-base imbalance are usually mixed, either enhancement or inhibition may occur. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance neuromuscular blockade

Drug/Laboratory Test Interactions: None known

Carcinogenesis, Mutagenesis, Impairment of Fertility: Studies in animals have not been performed to evaluate carcinogenic potential or impairment of fertility. Mutage studies (Ames test, Sister Chromatid Exchange) conducted with ARDUAN® revealed no ent of fertility. Mutagenia

Pregnancy Category C: A teratogenicity study has been conducted in rats using intravenously administered doses of ARDUAN® approximating the clinical dose in humans (50 μ g/kg). No teratogenic effects were observed in this study. An embryotoxic effect (secondary to maternal toxicity) was observed at the highest dose administered (50 μ g/kg) as demonstrated (50 μ g/kg) as demonstrated (50 μ g/kg). strated by an increase in earlier fetal resorptions. There are no adequate and well-controlled studies in pregnant women. ARDUAN® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Use in Obstetrics (cesarean section): There are insufficient data on placental transfer of ARDUAN® and possible related effect(s) upon the neonate following cesarean section delivery. In addition, the duration of action of ARDUAN® exceeds the duration of operative obstetrics (cesarean section). Therefore, ARDUAN® is not recommended for use in patients

Pediatric Use: Infants (3 months to 1 year) under balanced anesthesia (2 studies in 52 infants), or halothane anesthesia (1 study in 29 infants), manifest similar dose response to ARDUAN® as do adults on a μg/kg ABW basis. Children (1 to 14 years) under balanced anesthesia (4 studies in 57 children), or halothane anesthesia (2 studies in 29 children), may anesthesia (4 studies in 37 children), or naturation are an estimated (2 studies in 27 children), may be less sensitive than adults. These conclusions come from studies involving titrating patient response by the incremental method to approximately 1.2 times $ED_{\rm ss}$. There are no data on either onset time or clinical duration of larger doses in infants or children. There are no data on maintenance dosing in infants and children. Pharmacokinetic studies in infants and children in the control of the control on maintenance dosing in infants and children. Pharmacokinetic studies in infants and children have not been performed; therefore no pharmacokinetic modeling of incremental dosing can be attempted. The use of ARDUAN® in neonates and infants below 3 months of age has not been investigated. Antagonism has not been systematically studied in infants or children. However, usual clinical doses of neostigmine administered following significant levels of spontaneous recovery (recovery of 1, to more than 50% of control) produced complete antagonism of residual neuromuscular block in less than 10 minutes in the majority of cases.

ADVERSE REACTIONS: The most frequent side effect of non-depolarizing blocking coefficients and provided the size of the drug's pharmacolarizal proposal by the time.

agents as a class is an extension of the drug's pharmacological action beyond the time period needed for surgery and anesthesia. Clinical signs may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnea. This may be due to the drug's effect or inadequate antagonism.

The following listings are based upon U.S. clinical studies involving nearly 600 patients uti-

lizing a variety of premedications, varying lengths of surgical procedures, and various anes-

Adverse experiences in greater than 1% of cases and judged by the investigator to have a possible causal relationship: clinically significant hypotension (2.5% of cases); cli inficant bradycardia (1.4% of cases).

Adverse experiences in less than 1% of cases and judged by the investigator to have a

ssible causal relationship:

Cardiovascular: hypertension, myocardial ischemia, cerebrovascular accident, thrombosis, atrial fibrillation, ventricular extrasystole.

Metabolic and Nutritional: increased creatinine, hypoglycemia, hyperkalemia.

Musculoskeletal: muscle atrophy, difficult intubation.

Nervous: hypesthesia, CNS depression.

Respiratory: dyspnea, respiratory depression, laryngismus, atelectasis.

Skin and Appendages: rash, urticaria. Urogenital System: anuria.

HOW SUPPLIED: 10 mL vials containing 10 mg lyophilized pipecuronium bromide. Boxes of 6 (NDC 0052-0446-36) 10 mL vials containing 10 mg lyophilized pipecuronium bromid and 10 mL vials containing bacteriostatic water for injection, USP. Boxes of 6 (NDC 0052-0446-37)

Storage: 2°-30°C (36°-86°F). Protect from light.

After Reconstitution: When reconstituted with bacteriostatic water for injection, USP: CONTAINS BENZYL ALCOHOL, WHICH IS NOT INTENDED FOR USE IN NEWBORNS. Use within 5 days. May be stored at room temperature or refrigerated.

When reconstituted with sterile water for injection or other compatible IV solutions: Refrigerate vial. Use within 24 hours. Single use only. Discard unused portion.

REFERENCES

Data on file.
Foldes FF, Nagashima H, Nguyen HD, Duncalf D, Goldiner PL. Neuromuscular and cardiovascular effects of pipecuronium. Can J Anaesth. 1990;37(5):549-555.
Larijani GE, Bartkowski RR, Azad SS, et al. Clinical pharmacology of pipecuronium bromide. Anesth Analg. 1989;68:734-739.
Tassonyi E, Neidheart P, Pittet J-F, Morel DR, Gemperle M. Cardiovascular effects of nipecuronium and pancuronium in patients undergoing coronary artery bypass grafi pipecuronium and pancuronium in patients undergoing coronary artery bypass grafting. Anesthesiology. 1988;69(5):793-796.

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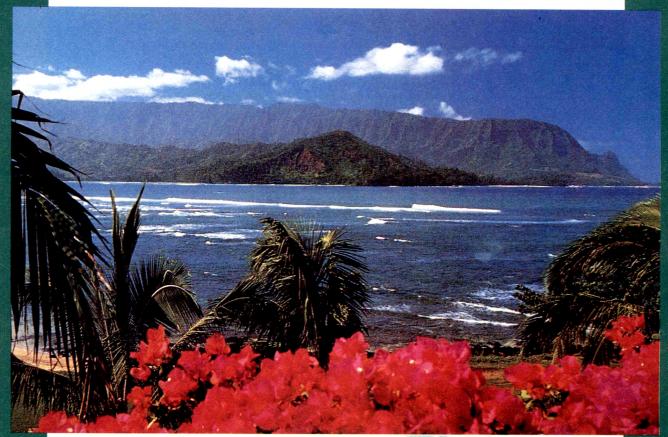
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S E C O N D



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Books for review should be sent directly to: Book Review Editor, Norig Ellison, MD, Department of Anesthesia, University of Pennsylvania, Philadelphia, PA 19104.



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CAUTION: Federal Law Prohibits Dispensing Without Prescription. **DESCRIPTION:** SUFENTA (sufentanii citrate) is a potent opioid analgesic chemically designated as N-[-4-(methoxymethyl)-1-[2-(2-thienyl)ethyl]-4-piperidinyl]-N-phenylpropanamide 2-hydroxy-1,2,3-propanetricarboxylate (11) with a molecular weight of 578.68. SUFENTA is a sterile, preservative free, aqueous solution containing sufentanii citrate equivalent to 50 μg per ml of sufentanil base for intravenous injection. The solution has a pH range

INDICATIONS AND USAGE: SUFENTA (sufentanil citrate) is indicated: As an analogsic adjunct in the maintenance of balanced general anesthesia. As a primary anesthetic agent for the induction and maintenance of anesthesia. As a primary anesthetic agent for the induction and maintenance of anesthesia to 100% oxygen in patients undergoing major surgical procedures, such as cardiovascular surgery or neurosurgical procedures in the sitting position, to provide favorable myocardial and cerebral oxygen balance or when extended postoperative ventilation is anticipated. SEE DOSAGE CHART FOR MORE COMPLETE INFORMATION ON THE USE OF SUFENTA.

CONTRAINDICATIONS: SUFENTA is contraindicated in patients with known hypersensitivity to the

CONTRAINDICATIONS: SUFENTA is contraindicated in patients with known hypersensitivity to the drug. WARNINGS: SUFENTA should be administered only by persons specifically trained in the use of intravenous anesthetics and management of the respiratory effects of potent opioids. An opioid antagonist, resuscitative and intubation equipment and oxygen should be readily available. SUFENTA may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is dose related. Administration of SUFENTA may produce muscular rigidity with a more rapid onset than that seen with fentanyl. SUFENTA may produce muscular rigidity that involves the skeletal muscles of the need and extremities. The incidence can be reduced by: 1) administration of SUFENTA at dosages of up to 8 µg/kg, 2) administration of all paralyzing dose of a neuromuscular blocking agent tollowing loss of consciousness when SUFENTA is used in anesthetic dosages (above 8 µg/kg) titrated by slow intravenous infusion, or 3) simultaneous administration of SUFENTA and a full paralyzing dose of a neuromuscular blocking agent when SUFENTA is used in anesthetic dosages (above 8 µg/kg). The neuromuscular blocking agent should be compatible with the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered SUFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

ventilation of patients administered SUFENIA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

PRECAUTIONS: General: The initial dose of SUFENTA should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. Vital signs should be monitored routinely. Nitrous oxide may produce cardiovascular depression when given with high doses of SUFENTA (see CLINICAL PHARMACOLOGY). The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxant required should be considered in the selection of a neuromuscular blocking agent. High doses of pancuronium may produce increases in heart rate during SUFENTA-oxygen anesthesia. Bradycardia has been reported infrequently with SUFENTA-oxygen anesthesia and has been responsive to atropine. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by SUFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CQ, stimulation which may persist into or recur in the post-operative period. Appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained prior to discharging the patient from the recovery area. Interaction with Other Central Nervous System Depressants: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when SUFENTA is administered to patients receiving barbiturates, tranquilitizers, other opioids, general anesthetics or other CNS depressants. In such cases of combined treatment, the dose of one or both agents should be reduced. Head Injuries: SUFENTA may obscure the clinical course of patients with hea decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, SUFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion

Or SOFENIA.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of SUFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats revealed that single intravenous doses of SUFENTA as high as 80 μg/kg (approximately 2.5 times the upper human dose) produced no

structural chromosome mutations. The Ames Salmonella typhimurium metabolic activating test also revealed no mutagenic activity. See ANIMAL TOXICOLOGY for reproduction studies in rats and rabbits.

Pregnancy Category C: SUFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects were most probably due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects have been observed after administration of SUFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. SUFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of SUFENTA in labor and delivery. Therefore, nended

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SUFENTA is administered to a nursing woman. Pediatric Use: The safety and efficacy of SUFENTA in children under two years of age undergoing cardiovascular surgery has been documented in a limited number of cases.

surgery has been documented in a limited number of cases.

Animal Toxicology: The intravenous Lp₂₀ of SUFENTA is 16.8 to 18.0 mg/kg in mice, 11.8 to 13.0 mg/kg in guinea pigs and 10.1 to 19.5 mg/kg in dogs. Reproduction studies performed in rats and rabbits given doses of up to 2.5 times the upper human dose for a period of 10 to over 30 days revealed high maternal mortality rates due to decreased food consumption and anoxia, which preclude any meaningful interpretation of the results.

ADVERSE REACTIONS: The most common adverse reactions of opioids are respiratory depression and skeletal muscle rigidity. The most frequent adverse reactions in clinical trials involving 320 patients administered SUFENTA were throatensing (796), hovertension (396), chest vall rigidity (396) and hardvacartia (396).

administered SUFENTA were: hypotension (7%), hypertension (3%), chest wall rigidity (3%) and bradycardia (3%). Other adverse reactions with a reported incidence of less than 1% were:

Cardiovascular: tachycardia, arrhythmia Gastrointestinal: nausea, vomiting Respiratory: apnea, postoperative respiratory

Dermatological: itching, erythema
Central Nervous System: chills
Miscellaneous: intraoperative muscle movement

DRUG ABUSE AND DEPENDENCE: SUFENTA (sufentanil citrate) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

OVERDOSAGE: Overdosage would be manifested by an extension of the pharmacological actions of SUFENTA (see CLINICAL PHARMACOLOGY) as with other potent opiniod analgesics. However, no experiences of overdosage with SUFENTA have been established during clinical trials. The intravengus LD₅₀ of SUFENTA in male rats is 9.34 to 12.5 mg/kg (see ANIMAL TOXICOLOGY for LD₅₀S in other species). Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with SUFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude more immediate countermoseure. respiratory depression bindowing overdosage with SPERVIA may be longer than the duration to action or the opinion antagonist. Administration of an opiniod antagonist should not preclude more immediates countermeasures. In the event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hyporentilation or apnea. A patent airway must be maintained, and a nasopharyngeal airway or endotrached tube may be indicated. If depressed respiration is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures may be employed.

DOSAGE AND ADMINISTRATION: The dosage of SUFENTA should be individualized in each case according to

body weight, physical status, underlying pathological condition, use of other drugs, and type of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of SUFENTA should betermined on the basis of lean body weight. Dosage should be reduced in elderly and debilitated patients (see PRECAUTIONS). Vital signs should be monitored routinely. Protect from light. Store at room temperature 15°-30° C

world leader in anesthesia research



March 1986, March 1987 U.S Patent No. 3,998,834 7618505-M

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Anesthesia and Analgesia

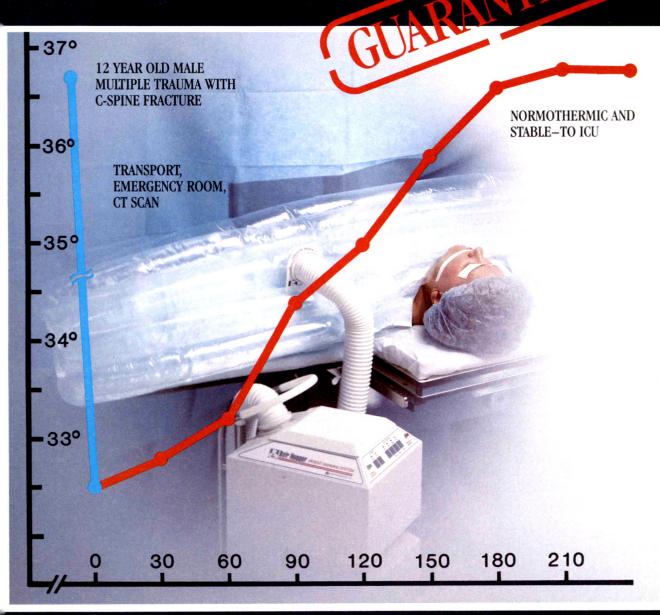
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1991 AWARDS

At the IARS 65th Congress in March 1991, the Board of Trustees announced recipients of the 1991 Award as follows:

Mitchell F. Berman, MD, Columbia University, New York, NY:

"Blockade of Cardiac Sodium Channels by Local Anesthetics. Whole-Cell and Single-Channel Analysis"

Alberto J. de Armendi, MD, AM, Massachusetts General Hospital, Boston, MA: "Mechanisms of Anaesthesia of Volatile and Barbiturate Anaesthetics at the Acetylcholine Receptor"

Stephen W. King, PhD, MD, University of California, San Francisco: "Anesthetic Effects on the Inositol Triphosphate Receptor"

Pontus Ostman, MD, The University of Iowa, Iowa City, IA:

"The Efficacy and Hemodynamic Effects of Epidurally Administered Dexmedetomidine Towards Visceral and Thermal Nociceptive Stimulus in the Gravid Guinea Pig"

Mark S. Scheller, MD, University of California, San Diego:

"Modifications of Patterns of Hippocampal Excitatory Amino Acid Concentrations Following Global Cerebral Ischemia in Rabbits by Two Voltage Dependent Calcium Channel Antagonists"

Margaret M. Sedensky, MD, Case Western Reserve University, Cleveland, OH: "Analysis of the Site(s) of Action of Volatile Anesthetics by Molecular Genetics"

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Neuromuscular blocking agents for the ICU: How do they compare?

		TRACRIUM	vecuronium	pancuronium
W.	Good cardiovascular profile in surgical patients?	YES	YES	NO (vagolytic) ¹
	Elimination half-life (based on single-dose kinetics)	20 minutes ² (approximate)	65 to 75 minutes ³	89 to 161 minutes ¹
	Nonhepatic/non- renal mode of elimination	YES	NO	NO
alla	unaltered by renal or hepatic dysfunction?	YES ^{2,6*}	NO significantly prolonged ³⁻⁶ *	NO ⁷ * doubled ¹
	Rapid recovery after infusion even in patients with renal failure?	YES 47 to 105 minutes in five renal failure patients after 15-37-hr. infusion ⁶	NO 6 to 37 hours in six renal failure patients after 7-32-hr. infusion ⁶	Infusion not recommended ⁷
	Ready-to-use convenience?	YES	NO requires reconstitution	YES



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mbdures, Trachum may be inactivated and a free acid may be precipitated. Their imminipation 10 mil multiple dose viets contrib hencys disordal, Bertzy elson'd has been associated with an increased incidence of neutropical and other complications in newtorn intains which are sometimes fatal. Trachum injection 5 mil ampuls and 5 mil stige use visia do not contain benzyl disorda.

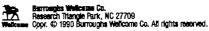
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month have not been established.

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4. Lynam DP, Cronnelly R, Castegnoll KP, Cantell C, Caldwell J, Arden J, et al. The pharmacodynamics and pharmocidenatics of vecuronium in patients anesthesized with isoflurane with normal renal function or with renal failure. Anaesthesiology, 1966;69:227-231.
5. Lebraulit C, Diveldestin P, Henzel D, Chauvin M, Queson P, Pharmacokinetics and pharmacology of vecuronium in patients with cholestasis. Sr J Anaesth 1966;68:983-987.
6. Hunter JM. Industons of stracultum and vecuronium in patients with multisystem organ failure in the intensive therapy until. Insights into Anaesthesiology, 1987;1:23-27.
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Cerebral Hemodynamics in Neonates and Infants Undergoing Cardiopulmonary Bypass and Profound Hypothermic Circulatory Arrest: Assessment by Transcranial Doppler Sonography

Simon C. Hillier, MB, FFARCS, Frederick A. Burrows, MD, FRCPC, Bruno Bissonnette, MD, FRCPC, and Robert H. Taylor, MB, FFARCS

HILLIER SC, BURROWS FA, BISSONNETTE B, TAYLOR RH. Cerebral hemodynamics in neonates and infants undergoing cardiopulmonary bypass and profound hypothermic circulatory arrest: assessment by transcranial Doppler sonography. Anesth Analg 1991;72:723–8.

Profound hypothermic circulatory arrest (PHCA) is followed by a transient period of increased intracranial pressure and a longer period of neurophysiologic dysfunction. To investigate the effect of cardiopulmonary bypass (CPB) with PHCA on cerebral hemodynamics, we used transcranial Doppler sonography to measure cerebral blood flow velocity in 10 neonates and infants before and after PHCA. Cerebral blood flow velocity was compared before and after PHCA during normothermic cardiopulmonary bypass at the same mean arterial pressure, central venous pressure, hematocrit, and arterial carbon dioxide tension. Cerebral

blood flow velocity decreased exponentially with decreasing nasopharyngeal temperature before PHCA (P < 0.05) and remained decreased after PHCA during normothermic CPB, compared with values for normothermic CPB before PHCA (P < 0.005). During normothermic CPB after PHCA, the modified cerebral vascular resistance (mm Hg·cm·s⁻¹) was increased above values for normothermic CPB before PHCA (P < 0.05). The results of this study suggest that the observed increase in intracranial pressure during PHCA is not caused by increased cerebral perfusion, but rather that cerebral perfusion is reduced in response to a decreased demand for cerebral metabolic oxygen.

Key Words: ANESTHESIA, PEDIATRIC. BRAIN, BLOOD FLOW. SURGERY, CARDIAC. MEASUREMENT TECHNIQUES, ULTRASOUND.

The use of cardiopulmonary bypass (CPB) with profound hypothermic circulatory arrest (PHCA) to facilitate the repair of congenital heart defects in infancy is accompanied by a definite incidence of neurologic sequelae, both transient and permanent (1–4). The period of CPB immediately after PHCA is associated with a transient increase in intracranial pressure (ICP), a decrease in cerebral perfusion pressure (CPP) (5,6), and the absence of neurophysiologic function (6). Although it is known that cerebral blood flow (CBF) is decreased after PHCA (7), no study has used real-time techniques to monitor cerebrovascular hemodynamics during the period of CPB immedi-

ately before and immediately after PHCA during the period of elevated ICP and absent neurophysiologic function.

To investigate the cerebrovascular hemodynamics of neonates and infants during CPB with PHCA, we used transcranial Doppler sonography to measure cerebral blood flow velocity (CBFV) in the basal cerebral vessels during corrective surgery for congenital cardiac defects.

Methods

With the approval of the Human Subject Review Committee, 10 patients less than 9 mo of age (range, 1–150 days) were studied after their admission to The Hospital for Sick Children in Toronto, Ontario, for surgical repair of congenital cardiac defects requiring CPB with PHCA. Patients were excluded if neurologic dysfunction was present before surgery.

Anesthesia was induced with 50–100 µg/kg intravenous fentanyl, and neuromuscular blockade was

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achieved with 0.15 mg/kg pancuronium. After nasotracheal intubation, controlled intermittent positive pressure ventilation and peak-inspiratory pressures of 20-25 cm H₂O were used to ventilate the lungs with an air/oxygen mixture. Positive end-expiratory pressure was avoided, and ventilation was adjusted to achieve normocarbia. Supplemental doses of fentanyl and pancuronium were administered as necessary. A preductal radial arterial catheter was inserted for measurement of systemic arterial pressure and for intermittent blood sampling. A central venous catheter was inserted percutaneously into the superior vena cava through the external or internal jugular vein to measure the central venous pressure (CVP). Rectal, esophageal, and nasopharyngeal temperatures were monitored. No cerebral vasoactive agents were administered.

After anticoagulation with 300 IU/kg heparin, nonpulsatile CPB was established with a standard roller pump (Cobe Canada Ltd., Scarborough, Ontario) and a 0.8- or 1.6-m² Capiox hollow fiber membrane oxygenator (Terumo, Tokyo, Japan). The CPB circuit was primed with packed red blood cells, 5% albumin, and Plasmalyte (Travenol, Mississauga, Ontario) solution plus (1 g/kg) mannitol to maintain a hematocrit of 25%-30% during CPB. Cardiopulmonary bypass flows were calculated as normal between 2.4 and 3.2 $L \cdot m^{-2} \cdot min^{-1}$. Cardioplegia consisted of modified Roe's solution (8), with 20 mEq/L of sodium bicarbonate solution, given in an initial dose of 300 mL/m² body surface area, then in 150-mL/m² doses at approximately 30-min intervals. Patients were cooled at a rate of 1-3°C/min until the nasopharyngeal temperature (NPT) was less than 16°C and the rectal temperature was less than 20°C before circulatory arrest. After circulatory arrest, the patients were reperfused and rewarmed at a rate of 1-3°C/min to normothermia (>36°C NPT) before separation from CPB.

Alpha-stat acid-base management was used (9). Paco₂ was maintained between 32 and 37 mm Hg, and pH between 7.35 and 7.40. Arterial blood gas tensions were measured with a Nova Stat Profile 5 blood-gas analyzer (Nova Biomedical, Waltham, Mass.). During CPB, arterial acid-base status was continuously monitored with a CDI 300 monitoring system (Cardiovascular Devices, Inc., Irvine, Calif.).

Throughout the study, mean arterial pressure (MAP), CVP, CBFV, and NPT were measured continuously. During each of the prebypass, cooling bypass, circulatory arrest, and warming bypass periods, nasopharyngeal, esophageal, and rectal temperatures were measured and recorded every 5 min, and arterial blood gas tensions and hematocrits were measured every 15 min.

Cerebral Blood Flow Velocity

Cerebral blood flow velocity was measured noninvasively by transcranial Doppler sonography with the transcranial Doppler TC 2-64B, EME (Carolina Medical Electronics Inc., King, N.C.). The transducer probe was placed over the anterior fontanel to display and monitor continuously the pericallosal portion of the anterior cerebral artery (ACA). A range-gated, pulsed-wave, Doppler probe (area = 1.5 cm^2) with a frequency of 2 MHz and a maximum intensity of 100-mW power to a depth of 25–120 mm was used. The reflected frequency spectra were displayed with an IBM AT2 computer interface to allow real-time visual interpretation of the CBFV waveform and optimal adjustment of the transducer position, gate depth, angle of insonation, emitted power, and dynamic range. Once an acceptable waveform was achieved, the transducer position was secured with an adjustable fixation device to maintain a constant angle of insonation to permit continuous measurement of CBFV. The frequency spectrum of Doppler signals was analyzed by fast Fourier transformation; Fourier pulsatility provided a precise spectral analysis of the displayed waveform. We used the envelope of the spectra to determine the CBFV within the ACA by positioning the cursor on the different peak-systolic and end-diastolic positions of four individual frequency outlines.

Data Analysis

The paired Student's *t*-test was used to compare measurements recorded at normothermia before and after PHCA. Comparisons were made at the same levels of NPT, MAP, CVP, hematocrit, Paco₂, and pH. Multiple pairwise comparisons were made with repeated measures analysis of variance and the Tukey post hoc multiple range test.

An index of cerebrovascular resistance, modified cerebrovascular resistance (MCVR), was calculated using the equation

MCVR (mm
$$Hg \cdot cm \cdot s^{-1}$$
) = (MAP - CVP)·CBFV⁻¹

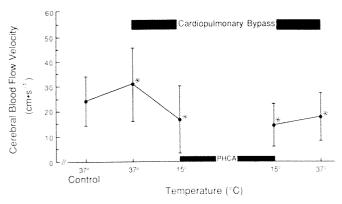
at normothermia before and after PHCA and compared with Student's paired t-test. Nonlinear regression analysis was performed between CBFV and NPT, and the Q_{10} (the ratio of metabolic rates at two temperatures separated by 10° C) was calculated.

Statistical significance was accepted as P < 0.05. Data are expressed as mean \pm standard deviation (sD).

Table 1.	Demographic	and	Circulatory	Arrest Data
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Patient	Diagnosis	Procedure	Age (days)	Weight (kg)	Duration of PHCA (min)	PHCA temp (°C)
1	VSD	Complete repair	28	3.4	59	14
2	HLHS	Norwood stage I	1	3.5	60	14
3	IAA	Complete repair	20	3.5	68	15
4	AVSD	Complete repair	150	4.7	53	15
5	VSD	Complete repair	150	3.9	32	14
6	TGA	Arterial switch	3	3.4	25	15
7	TGA	Arterial switch	3	3.8	37	16
8	TA	Complete repair	42	2.8	23	17
9	TGA	Arterial switch	21	3.5	75	18
10	TAPVR	Complete repair	19	2.1	48	16

VSD, ventricular septal defect; HLHS, hypoplastic left-heart syndrome; IAA, interrupted aortic arch; AVSD, atrioventricular septal defect; TGA, transposition of the great arteries; TA, truncus arteriosis; TAPVR, total anomalous pulmonary venous return; PHCA, profound hypothermic circulatory arrest.



<u>Figure 1</u>. Changes in CBFV before CPB and before and after PHCA at normothermia and profound hypothermia. Values represent mean \pm sp. *P < 0.05 compared with control.

Results

Demographic data, diagnosis, and details of the surgical procedures performed for the 10 patients are displayed in Table 1. The ages of the patients ranged from 1 to 150 days (43.7 \pm 57.5 days, mean \pm sD) and weights from 2.1 to 4.7 kg (3.45 \pm 0.68 kg). The patients were cooled to a mean NPT of 15.4 \pm 1.4°C before the institution of PHCA. The duration of PHCA was 48 \pm 18 min.

There was no significant difference between the MAP, CVP, hematocrit, $Paco_2$, and pH levels for CBFV measurements taken during normothermic CPB before and after PHCA. The changes in CBFV with the onset of CPB and at normothermic and hypothermic CPB before and after PHCA are presented in Figure 1 and Table 2. Cerebral blood flow velocity increased significantly from that taken before the CPB control (23.9 \pm 9.8 cm/s) because the patients were placed on normothermic CPB (30.6 \pm 14.6 cm/s). However, the values obtained before the initiation of CPB could not be controlled for the MAP, CVP, hematocrit, Paco₂, and

pH. During systemic cooling on CPB, CBFV decreased as NPT decreased. The relationship was best described by an exponential curve with a correlation coefficient (r) of 0.78 (Figure 2). The ratio of the CBFV to the NPT was determined between 37°C and 27°C (1.7 \pm 0.12) and between 27°C and 17°C (2.1 \pm 0.32) and compared with published values for CBF and Q₁₀.

There was no significant difference in the CBFV immediately before and immediately after PHCA. During systemic rewarming after PHCA, the CBFV remained low, and, at normothermia, it was not significantly different from what it was immediately after PHCA. In comparison with the CBFV during normothermic CPB before PHCA, there was a highly significant (P < 0.005) decrease in CBFV during normothermic CPB after PHCA ($30.6 \pm 14.6 \text{ vs } 17.6 \pm 9.4 \text{ cm/s}$, respectively) when MAP, CVP, hematocrit, Paco₂, and pH were held constant (Figure 3).

The MCVR was calculated during normothermic CPB before and after PHCA. The MCVR at normothermia after PHCA was significantly greater than that at normothermia before PHCA (Figure 4).

In all but three patients (subjects 2, 3, and 6, Table 1), detectable CBFV returned immediately upon reperfusion after PHCA. The return of detectable perfusion was delayed for up to 3 min in these three patients despite appropriate systemic pump flows and perfusion pressures.

Discussion

We have shown that CBFV is reduced and MCVR is increased in neonates and infants immediately after PHCA, and that each remains reduced and increased, respectively, for the duration of the procedure. This finding is unexpected because previous work in dogs (10) has demonstrated a stage of reperfusion hyper-

Table 2.	Hemod	vnamic	Data	During	Surgery

Hemodynamic		CPB before PHCA		CPB after PHCA	
data	Control before CPB	37°C	15°C	15℃	37°C
MAP (mm Hg)	42.8 ± 4.3	40.7 ± 3.5	39.8 ± 4.2	45.0 ± 9.5	43.0 ± 6.1
CBFV (cm/s)	23.9 ± 9.8	30.6 ± 14.6	16.4 ± 13.2	14.4 ± 8.2	17.6 ± 9.4
Paco ₂ (mm Hg)	31.8 ± 4.5	30.5 ± 5.4	31.6 ± 5.4	29.7 ± 4.9	30.1 ± 5.2
Hct (%)	35.6 ± 6.1	27.0 ± 2.3	26.9 ± 2.1	26.1 ± 2.4	26.3 ± 2.0
CVP (mm Hg)	7.8 ± 3.4	3.2 ± 3.1	1.3 ± 3.9	1.5 ± 5.4	1.2 ± 3.3

CPB, cardiopulmonary bypass; PHCA, profound hypothermic circulatory arrest; MAP, mean arterial pressure; CBFV, cerebral blood flow velocity; Hct, hematocrit; CVP, central venous pressure.

All data are expressed as mean ± sp.

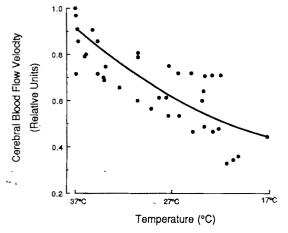


Figure 2. The exponential relationship between NPT and CBFV during cooling before PHCA (r = 0.78).

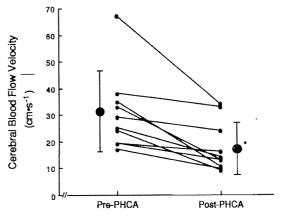


Figure 3. The change in CBFV when measured during normothermic CPB before and after PHCA. *P < 0.005.

emia before a stage of hypoperfusion after a period of complete cerebral ischemia.

Our use of CBFV as an index of cerebral perfusion is based on previous work that has demonstrated that the basal cerebral vessels remain constant in caliber despite variation in either the Paco₂ or the CPP (11-13). Several assumptions underlie the relationship between CBFV, as measured with transcranial

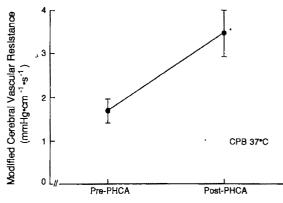


Figure 4. The change in calculated cerebrovascular resistance measured during normothermic CPB before and after PHCA. *P < 0.05.

Doppler sonography, and CBF. First, we assumed that changes in CBFV were proportional to changes in CBF. Data collected with range-gated, pulsed transcranial Doppler sonography in adults showed a close correlation with other established techniques used to measure CBF (r = 0.80-0.93) (14).

Second, we assumed that the diameter of the ACA remains constant throughout the study period. Angiographic studies of the basal cerebral arteries in adults have shown that the diameters of the large vessels remain relatively constant during changes in Paco₂ (15). The site of major cerebrovascular resistance changes appears to be downstream from the basal cerebral vessels, as confirmed by measurements of the vasoconstrictive and vasodilating responses to changes in Paco2 or other extrinsic physiologic factors (16). It has been shown that while Petco2 increased from 20 to 60 mm Hg, CBFV did not decrease but actually increased logarithmically, whereas cerebrovascular resistance decreased with increasing Petco₂ (17). This reciprocal change may be explained by the hypothesis that the arterioles were dilated and that CO₂ did not significantly affect the diameter of the middle cerebral artery.

Third, we assumed that the angle of insonation remains constant during the study period. In this study, the Doppler probe was fixed in place to minimize variability in measurements between individuals. Previous investigators (11) have shown that the angle between the ultrasound beam and the flow of blood must be minimized to decrease the error in velocity measurement. Because the velocity of the blood flow is proportional to the cosine of the angle of insonation, as the angle approaches 0° the cosine approaches 1.0. The maximum error that may be attributed to the change in the angle of insonation is 13% at an angle of 30°. Blood flow in the ACA of the pericallosal portion is oriented toward the ultrasound probe, and therefore if the vessel diameter, the angle of Doppler insonation, and the flow characteristics within the vessel are constant, the changes recorded will reflect changes in CBF. The comparisons of CBFV during CPB were made during nonpulsatile CPB at similar MAP, CVP, Paco₂, pH, and hematocrit; therefore, changes in flow characteristics are unlikely. The use of transcranial Doppler sonography as an index of cerebral perfusion during CPB in children undergoing major cardiac surgery has been reported previously (18), and other studies (14) have demonstrated that changes in CBFV correlate well with changes in CBF.

The MCVR can be used as an index of cerebrovascular resistance because of the relationship between CBF and CBFV (14). The calculation of MCVR using MAP as an indicator of the CPP during CPB can be misleading. In adults with continuous monitoring of MAP, CVP, and ICP (through an epidural intracranial pressure monitor), MAP - CVP gives a fairly accurate estimate of CPP (19,20). In neonates and infants, however, a transient period of elevated ICP occurs on reperfusion immediately after PHCA (5). Therefore, in the present study CPP was not estimated during the initial period of reperfusion after PHCA because ICP monitoring was not performed in these patients. The use of MAP – CVP to calculate CPP in the present study would result in an overestimation of the CPP during the initial phase of reperfusion after PHCA. However, the use of MAP – CVP to calculate the CPP after the ICP has normalized would concur with the approach Lundar et al. (18) used. Previous studies (5,6) have suggested that the ICP returns to baseline values approximately 20 min after reestablishment of CPB after PHCA. Therefore, we calculated the CPP and MCVR during CPB at normothermia before and after PHCA. Because MAP and CVP were equal at both measurement periods, the MCVR reflects only changes in the CBFV, which we attribute to changes in cerebrovascular resistance.

The increase in CBFV after CPB is not surprising

because MAP, CVP, hematocrit, Paco₂, and pH could . not be controlled before CPB, and because the flow pattern changed to a nonpulsatile pattern. The decrease in CBFV after PHCA that we observed supports the results of the work of Greeley et al. (7), who used 131Xe clearance to measure global CBF after. PHCA. Although it is unclear from our results whether this lower CBFV is associated with cerebral ischemia, because cerebral oxygen supply and demand were not measured, a decrease in cerebral metabolic rate for oxygen (CMRo₂) (21) and an increase in oxygen availability (21,22) after PHCA have been demonstrated in neonates and infants. The reduction in CBFV may be the appropriate result of a decreased metabolic requirement for oxygen or, alternatively, may indicate a decrease in cerebral perfusion and oxygen supply, secondary to the elevation in ICP and decrease in CPP that result in the neurophysiologic dysfunction previously described (6,23) and a decreased demand for oxygen. Further study is necessary to investigate the cause of this reduction in CBFV.

Although the ratio of the decrement in CBFV from 37°C to 27°C during cooling was less than expected from published Q_{10} values for primates (24), our results concur with published ratios for CBF during similar degrees of cooling in children, who also demonstrated a greater calculated Q_{10} (21). These results and our own data suggest that some uncoupling of CBF from CMRo₂ occurs during the induction of hypothermia. These results are further supported by the work of Kurth et al. (22). They have suggested that the increase they found in cerebral oxygenation during the cooling period before PHCA implies a luxury perfusion state. This alteration in the CBF/CMRo₂ coupling may be due to the institution of nonpulsatile flow or hemodilution, or it may be artifactual, indicating the inability of NPT measurement to accurately reflect rapidly changing cerebral temperature.

The calculated MCVR did not change significantly with the onset of CPB because the increase in CBFV was offset by the decrease in CVP (Table 2). The lack of change in MCVR represents the maintenance of CBF/CMRo₂ coupling (25). The cause of the prolonged increase in MCVR after PHCA is not clear, but the increase could represent an appropriate response to decreased CMRo₂. Previous studies at our institution involving visual evoked potentials have documented the occurrence of a prolonged period of neurophysiologic dysfunction after PHCA (6,23). Studies of cerebral oxygenation with dual wavelength reflectance spectroscopy during CPB and PHCA (22) have been unable to demonstrate any evidence of

cerebral ischemia immediately after PHCA, although cerebral oxygen stores may have been reduced during the later stages of PHCA. Other studies (21) have demonstrated that levels of both CBF and CMRo₂ remained reduced for a prolonged period of time following rewarming after PHCA. These studies suggest that flow is reduced secondarily to decreased CMRo₂ because of a metabolic disturbance in oxygen use.

The cause of the delayed return of flow in three of our patients is unclear. Although MAP was thought to be adequate in all three, a transient elevation in ICP, followed by a subsequent fall in CPP, immediately after the reestablishment of a patient on CPB after a period of PHCA, has been documented (5,6). It is possible that during this period, the CPP was inadequate for cerebral perfusion in these patients. Further study is required.

In conclusion, the increased ICP after PHCA is not the result of increased cerebral perfusion, as indicated by the CBFV. The CBFV decrease and the MCVR increase after PHCA appear to be normal responses to the decrease in CMRo₂ (21) and could account for the observed neurophysiologic dysfunction. The previously described relationship between the duration of elevated ICP and the latency of return of the visual evoked potentials after a period of PHCA (6) may be solely temporal and not causative. The hypothesis that a change in intracranial blood volume, possibly by venous engorgement, produces the elevated ICP has yet to be investigated.

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Preoperative and Intraoperative Predictors of Inotropic Support and Long-Term Outcome in Patients Having Coronary Artery Bypass Grafting

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ROYSTER RL, BUTTERWORTH JF IV, PROUGH DS, JOHNSTON WE, THOMAS JL, HOGAN PE, CASE LD, GRAVLEE GP. Preoperative and intraoperative predictors of inotropic support and long-term outcome in patients having coronary artery bypass grafting. Anesth Analg 1991;72:729–36.

The prognostic value of preoperative symptoms, preoperative left ventricular function, and intraoperative factors as related to postoperative outcome in coronary artery bypass grafting is unclear. This study was performed to identify risk factors that could be used as markers to predict immediate and long-term outcome, knowledge of which might allow physicians to modify these factors to decrease the likelihood of an adverse outcome. We retrospectively evaluated preoperative factors (including age, sex, New York Heart Association [NYHA] classification of symptoms, ejection fraction [EF], wall motion abnormalities, baseline left ventricular end-diastolic pressure [LVEDP], postradiographic contrast injection LVEDP, change in LVEDP with contrast injection, cardiac enlargement, and collateral vessels) and intraoperative factors (duration of bypass and aortic cross-clamp time) in 128 patients. The need for inotropic drug support was used as a marker of immediate outcome. A 36-mo follow-up used death and the postoperative NYHA classification of symptoms as markers of long-term outcome. The various factors associated with the use of inotropes and immediate outcome were analyzed by logistic regression. The factors related to inotrope use

(and presumed adverse short-term outcome) in order of decreasing significance were lower EF, older age, cardiac enlargement, female sex, and higher baseline and postcontrast LVEDP. Patients with EF ≥ 55%, but also having wall motion abnormalities and LVEDP change ≥ 10 mm Hg, and all patients with EF < 55% were more likely to require inotropic drug stimulation after cardiopulmonary bypass. Neither the change in LVEDP nor the presence of wall motion abnormalities independently predicted the need for postoperative inotropic support. Analysis of long-term outcome in 113 patients revealed an improvement in mean NYHA score from 2.8 \pm 0.9 (mean \pm sD) preoperatively to 1.6 ± 0.7 postoperatively. Those factors that predicted a worse long-term outcome (defined as higher postoperative NYHA scores or death) were higher preoperative NYHA scores, older age, female sex, and prolonged duration of cardiopulmonary bypass. Only 5 of 113 patients had died at the 36-mo follow-up, precluding statistical analysis of mortality. In contrast to randomized trials of oral inotropic agents in chronic congestive heart failure, in this study the perioperative use of inotropes (our marker of immediate outcome) was only marginally predictive of a less favorable long-term outcome.

Key Words: ANESTHESIA, CARDIOVASCULAR. SURGERY, CARDIOVASCULAR—coronary artery bypass grafting.

Postoperative left ventricular dysfunction is common after coronary artery bypass surgery (1) and is related

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to the degree of preoperative left ventricular dysfunction, the duration (1) and quality of extracorporeal perfusion (2) and myocardial preservation (3), and the adequacy of the surgical repair (4). The ejection fraction (EF), as measured from biplane left ventriculography, is the most popular parameter for describing systolic cardiac function, and is an important predictor of survival in patients with coronary artery disease (5) and of morbidity and mortality from coronary artery bypass surgery (6,7). However, the relationship between EF and other preoperative mea-

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surements, including left ventricular end-diastolic pressure (LVEDP), wall motion abnormalities (WMA), cardiac enlargement, and the degree of post-operative left ventricular dysfunction, is not well defined. The preoperative EF as well as the presence of two or more segmental WMA may correlate with postoperatively depressed biventricular function curves in patients undergoing myocardial revascularization (8). It would be helpful preoperatively to determine, in patients with normal EF, whether WMA or an elevated LVEDP or a large change in LVEDP after radiographic contrast injection would predict clinically significant postoperative left ventricular dysfunction and outcome.

The requirement for postoperative inotropic drug support may be a marker for immediate negative outcome. Because it indicates poor or deteriorating ventricular function, many believe that the need for inotropic drug support implies a worse long-term outcome. We asked, therefore, by using logistic regression analysis, what patient demographic and cardiac catheterization data and what operative features are most closely associated with the need for inotropic drug support after coronary artery bypass grafting. Additionally, we analyzed by logistic regression whether any of these factors, including inotropic support, was a marker for adverse long-term outcome using the New York Heart Association (NYHA) symptom classification and death as the outcome events.

Methods

Data were collected retrospectively on 128 patients undergoing coronary artery bypass grafting with no fewer than two distal coronary anastomoses. Data collected included age, sex, NYHA score, baseline LVEDP and postcontrast LVEDP, and a number of radiographic assessments performed during left ventriculography and coronary angiography, including the presence of regional WMA (including hypokinesia, akinesia, and dyskinesia), cardiac enlargement (based on volumetric calculations), and the presence of collateral circulation. All cardiac catheterization measurements and calculations were performed by cardiologists. Intraoperative data collected included duration of cardiopulmonary bypass (pump time), duration of aortic cross-clamping (ischemic time), and whether inotropic support was administered to the patient. The attending anesthesiologists and surgeons were not aware of the study. Patients were judged to have required inotropic drug support if they received an inotrope (e.g., dopamine, dobutamine, epinephrine) in the operating room and for at least 12 h in the intensive care unit. Dopamine administered at low doses (0.5–3.0 μ g·kg⁻¹·min⁻¹) to increase urinary output was not considered inotropic stimulation. All patients received fentanyl (50–100 μ g/kg) as the basal anesthetic.

Data were statistically analyzed by logistic regression to determine which patient characteristics were jointly associated with the need for postoperative inotropic support (i.e., positive or negative association with immediate adverse outcome). Using this approach, the log of the odds of receiving inotropic support is modeled as a linear function of the other variables (i.e., $\ln [p/(1-p)] = BX = B_0 + B_1X_1 + B_2X_2 + \ldots$, where p is the probability of having inotropic support, X_i represents a patient characteristic, and B_i denotes the effect of that factor).

To classify more accurately the progression from good left ventricular function to bad left ventricular function, we divided the patients into the following three groups based on EF, WMA, and the change in LVEDP: group 1, EF \geq 55% and no WMA; group 2, EF \geq 55% and WMA; group 3, EF < 55% and WMA. These groups were further subdivided into subgroups A and B based on LVEDP changes of <10 mm Hg (A) or \geq 10 mm Hg (B) after contrast injection for ventriculography. Logistic regression was then applied to see if these classifications were predictive of the need for postoperative inotropic support and outcome after adjusting for other covariates. Differences between the groups were tested with the Kruskal–Wallis test.

Approximately 36 mo after surgery, each patient or family was contacted by telephone and the postoperative NYHA score or patient death was recorded. The NYHA score was recorded as follows: one point—no symptoms; two points—mild symptoms with normal exercise; three points—symptoms with mild exercise; four points—symptoms at rest. Long-term outcome data were analyzed using preoperative and postoperative NYHA scores for 113 patients by univariate and multivariate logistic regression analysis of postoperative NYHA scores and univariate logistic regression analysis of death.

Results

Short-Term Outcome Analysis

Descriptive statistics for patient characteristics classified by the need for inotropic support are shown in Table 1. Those factors univariately associated with inotropic support were lower EF, older age, cardiac enlargement, female sex, and higher baseline and

Table 1. Patient Characteristics Associated With the Use of Inotropic Drug Support

Variable	No inotropic drug support $(n = 58)$	Inotropic drug support $(n = 70)$	P
variable		(11 - 70)	
Age (yr)	57 ± 8	62 ± 8	0.005
Sex			
Female (%)	10	26	0.027
Male (%)	90	74	
Collateral circulation (%)	64	73	0.271
WMA (%)	78	84	0.334
Patients demonstrating	7	21	0.021
cardiac enlargement (%)			
Baseline LVEDP (mm Hg)	14 ± 7	16 ± 6	0.044
Postcontrast LVEDP (mm Hg)	21 ± 8	24 ± 7	0.054
Change in LVEDP (mm Hg)	7 ± 6	7 ± 7	0.534
EF (%)	61 ± 11	54 ± 13	0.002
PT (min)	106 ± 30	125 ± 37	0.004
IT (min)	42 ± 15	50 ± 19	0.009

WMA, wall motion abnormalities identified during preoperative radiographic-contrast ventriculography; LVEDP, left ventricular end-diastolic pressure; EF, preoperative ejection fraction calculated from end-diastolic and end-systolic measurements from radiograph-contrast ventriculography; PT, total duration of cardiopulmonary bypass (pump time); IT, duration of aortic cross-clamping (ischemic time).

All values except for sex, collateral circulation, WMA, and patients demonstrating cardiac enlargement are expressed as mean ± sp.

Table 2. Comparison of Selected Variables in the Six Groups of Patients Classifying Ventricular Function

	LVEDP change < 10 mm Hg (A)			LVEDP changes ≥ 10 mm Hg (B)			,
	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3	· • · P
n	16	34	28	8	22	20	
Age (yr)	60 ± 8	59 ± 9	60 ± 10	63 ± 9	60 ± 6	61 ± 9	0.95*
Sex					•		•
Female (%)	0	12	11	25	36	35	0.02 ^b
Male (%)	100	88	89	· 75	64	65	
Collateral circulation (%)	50	56	<i>7</i> 1	63	82	90	0.04^{b}
Cardiac enlargement (%)	0	3	25	12	9	4 0	< 0.01 ^b
Resting LVEDP (mm Hg)	15 ± 5	16 ± 6	18 ± 8	13 ± 6	13 ± 5	15 ± 7	0.06"
Pump time (mm Hg)	119 ± 36	116 ± 34	115 ± 31	121 ± 38	122 ± 43	112 ± 36	0.98
Ischemic time (mm Hg)	44 ± 19	46 ± 17	45 ± 20	41 ± 13	52 ± 17	50 ± 18	0.494

LVEDP, left ventricular end-diastolic pressure.

postcontrast LVEDP. The presence of collateral vessels, WMA, and change in LVEDP did not independently correlate with the need for postoperative inotropic therapy.

The analysis of the six groups based on EF, WMA, and LVEDP is summarized in Table 2 and Figure 1. Table 2 lists the comparison of selected variables between the groups. Collateral coronary circulation and cardiac enlargement were more prevalent in patients with LVEDP change ≥ 10 mm Hg and in patients with poor left ventricular function. There were also more female patients in the LVEDP change ≥10 mm Hg group. There were no significant differences between groups comparing age, resting LVEDP, pump time, and ischemic time using the Kruskal–Wallis test.

The incidence and percentage of patients in each group requiring postoperative inotropic support are presented in Figure 1 and Table 3. Logistic regression analysis was used to assess the effects of WMA, EF, change in LVEDP, and their interaction, controlling for sex, age, resting LVEDP, pump time, ischemic time, collateral circulation, and cardiac enlargement. Because of interaction between group and LVEDP change, separate logistic regression analyses were conducted for each group (1, 2, or 3) and each subgroup (A or B) within each group. Of the three WMA/EF groups, only group 2 (P = 0.007) revealed a significant difference in LVEDP change, with subgroup 2B requiring more inotropic support than subgroup 2A. Only in patients with LVEDP change < 10 mm Hg (subgroup A) can ejection fraction be used

Values for age, resting LVEDP, pump time, and ischemic time are expressed as mean ± sp.

Based on Kruskal-Wallis test.

^bBased on χ^2 -analysis.

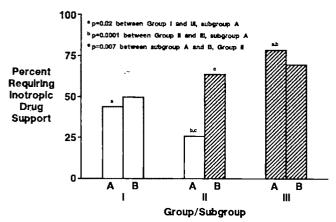


Figure 1. Association between preoperative contrast-induced change in LVEDP, EF, and WMA and the incidence of postoperative inotropic drug support. Statistical comparisons are made only within groups (1, 2, or 3, comparing subgroups A versus B) or subgroups (A or B, comparing groups 1, 2, or 3). Statistical analyses separated the patients into those with low (clear bars) and high (striped bars) probability of requiring inotropic drug support. There were no group or subgroup differences comparing the high or low probability classification. (Group $1 = EF \ge 0.55$, no WMA; group $2 = EF \ge 0.55$, WMA; group 3 = EF < 0.55, WMA; subgroup A = LVEDP change < 10 mm Hg; subgroup B = LVEDP change ≥ 10 mm Hg).

<u>Table 3</u>. Proportion of Patients Receiving Inotropic Support Based on Ejection Fraction and Duration of Cardiopulmonary Bypass

	7 71			
EF (%)	PT (min)	n	Inotropic support (%)	P
27–45	48–100	10	100	
	101-150	6	83	NSª
	151-195	7	71	
46-65	48100	26	35	
	101-150	34	47	<0.05
	151-195	14	<i>7</i> 9	
66-85	48-100	15	33	
	101-150	10	30	< 0.05
	151–195	6	100	

EF, ejection fraction; PT, duration of cardiopulmonary bypass; NS, not significant.

to predict inotropic support (P < 0.001). Among patients with LVEDP change < 10 mm Hg, pairwise comparisons revealed significant differences between subgroups 1A and 3A (P = 0.023) and between subgroups 2A and 3A (P = 0.0001) using a sequentially rejective Bonferroni adjustment to maintain an overall 0.05 significance level. Therefore, group 1 (EF \geq 55%, without WMA) and group 2A (EF \geq 55%, WMA, and LVEDP change < 10 mm Hg) had similar outcomes with a reduced need for inotropic therapy compared with group 2B (EF \geq 55%, WMA, and LVEDP change \geq 10 mm Hg) and group 3 (EF < 55%,

<u>Table 4</u>. Factors That Predict Higher Postoperative New York Heart Association Symptom Scores

Independent variable	P
Pre-NYHA	0.013
Pre-NYHA and	
Age	0.009
Sex	0.017
CE	0.909
Collaterals	0.243
WMA	0.094
EF	0.268
Baseline LVEDP	0.106
Postcontrast LVEDP	0.439
Change in LVEDP	0.583
Inotropes	0.094
PT	0.009
IT	0.120
Groups (six subgroups)	0.903

Pre-NYHA, preoperative New York Heart Association symptom classification (see text for details); CE, cardiac enlargement; WMA, wall motion abnormalities; EF, left ventricular ejection fraction at cardiac catheterization; LVEDP, baseline left ventricular end-diastolic pressure during cardiac catheterization; postcontrast LVEDP, LVEDP measurement after ventriculorgaphy during catheterization; change in LVEDP, postcontrast LVEDP baseline LVEDP; PT, duration of cardiopulmonary bypass; IT, duration of aortic cross-clamping.

WMA), both of which had a greater need for inotropic support and a worse outcome.

All of the variables in Table 1 and their two-way interactions were included in a forward-stepping algorithm that, at each step, adds the variable contributing most to the significance of the model. Ejection fraction was the first variable to enter the model, followed by pump time, the interaction between EF and pump time, age, and sex. For patients with poor preoperative left ventricular function (EF \leq 45%), pump time did not predict the need for inotropic support; more than 70% of these patients needed inotropic support (Table 4). Conversely, for patients with better ventricular function (EF \geq 46%), the need for inotropic support correlated with increasing pump time.

Long-Term Outcome Analysis

Long-term outcome analysis with a frequency comparison of preoperative versus 36-mo postoperative NYHA scores is illustrated in Figure 2. Most patients (n = 94, 83%) had a decrease (improvement) from preoperative to postoperative NYHA scores. Fourteen patients (12%) had no change in preoperative to postoperative NYHA score, and five patients (4%) had a higher postoperative NYHA score. The mean preoperative NYHA score was 2.82 ± 0.86 (mean \pm

[&]quot;Analyzed using χ^2 .

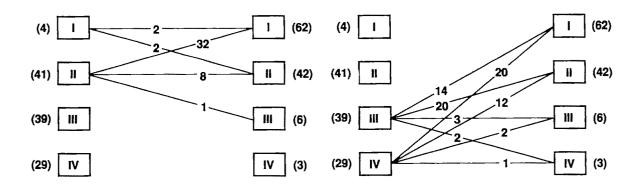


Figure 2. Left panel: changes in the NYHA symptom classification I and II from preoperative (left column) to the 36-mo postoperative follow-up. Right panel: changes in the NYHA classification III and IV from preoperative (left column) to the 36-mo postoperative follow-up. The mean preoperative NYHA score was 2.82 ± 0.86 compared with a postoperative NYHA score of 1.56 ± 0.72 . The numbers in parentheses represent the total number of patients in each classification preoperatively (left column) and postoperatively (right column) in each panel.

sD) compared with a postoperative NYHA score of 1.56 ± 0.72 .

A covariance model selection procedure was used to select the set of variables that best describes the 36-mo postoperative NYHA scores (Table 4). The variables for selection included the preoperative NYHA score in addition to a step-by-step insertion of independent variables. Preoperative NYHA scores (P = 0.013), older age (P = 0.009), female sex (P = 0.017), and longer pump times (P = 0.009) predicted adverse long-term outcome and higher postoperative NYHA scores.

Five patients in this data set (4%) had died by the 36-mo follow-up. Three of four patients were male; three had WMA; three had cardiac enlargement. Patients who died appeared to be slightly older and had higher preoperative NYHA scores (all nonsignificant). Logistic regression models were fitted to determine the effect of baseline characteristics on the odds of death. The logistic regression analysis had difficulty detecting significant relationships between these variables and the odds of death owing to both the small sample size and the small number of deaths. The only variable of marginal significance was higher preoperative NYHA score (P = 0.086, Table 5). Multivariable logistic regression analysis was not feasible because of the results of the univariate analyses.

Discussion

The outcome from coronary artery bypass grafting can only be improved by identifying reversible risk factors related to postoperative morbidity and mortality. As in noncardiac surgery (9-11), various risk factors have been defined for cardiac surgery, many of which are not alterable. Moreover, these risk factors have changed over the last two decades, probably related to improved surgical techniques and a changing patient population (12). The most recent identifiable risks for myocardial revascularization include age, congestive heart failure, an abnormal electrocardiogram, small body surface area, and incomplete revascularization (12-14). Despite an increasing population of older and sicker patients being admitted for surgery, the overall mortality of coronary artery bypass grafting continues to decline (14). Further decline in operative morbidity and mortality will require more studies that aggressively identify additional risk factors that may be modifiable, as in ongoing studies involving two-dimensional transesophageal echocardiography and perioperative ischemia (15).

Acute myocardial dysfunction occurs commonly after cardiac surgery and may be especially significant in patients with preoperative ventricular dysfunction (1,16,17). The need for inotropic drug support after cardiac surgery is a marker of clinically significant ventricular dysfunction and an adverse short-term outcome. Preoperative risk factors in our study that predicted an adverse short-term outcome included EF, the most robust predictor (P = 0.0022), followed by older age, female sex, and cardiac enlargement. We suspect that female sex predicts a worse outcome as a consequence of the association between small body surface area (a marker of adverse outcome in the Coronary Artery Surgery Study [CASS]) and female sex (18). The intraoperative factors of duration of cardiopulmonary bypass and duration of the myocardial ischemic period also were significantly related to the need for inotropic drug support. It is interesting that the duration of cardiopulmonary bypass was more predictive of an adverse short-term outcome in patients with better ventricular function (EF \geq 46%). Theoretically, the hypokinetic and akinetic segments

<u>Table 5</u>. Factors That Predict Death Within 36 mo of Coronary Artery Bypass Grafting

Independent variable	P
Pre-NYHA score	0.086
Age	0.223
Sex	0.753
CE	0.574
Collaterals	0.430
WMA	0.753
EF	0.259
LVEDP	0.551
Postcontrast LVEDP	0.946
Change in LVEDP	0.337
Inotropic drug support	0.859
PT	0.704
П	0.394
Groups (six subgroups)	0.659

Pre-NYHA, preoperative New York Heart Association symptom classification (see text for details); CE, cardiac enlargement; WMA, wall motion abnormalities; EF, left ventricular ejection fraction at cardiac catheterization; LVEDP, baseline left ventricular end-diastolic pressure during cardiac catheterization; postcontrast LVEDP, LVEDP measurement after ventriculography during catheterization; change in LVEDP, postcontrast LVEDP baseline LVEDP; PT, duration of cardiopulmonary bypass; IT, duration of aortic cross-clamping.

that result from severe stenoses or total coronary occlusions (frequently associated with reduced ventricular function) may protect those areas of myocardium from the pathophysiologic events (hemodilution, hypothermia, nonpulsatile flow) of cardiopulmonary bypass. However, the greater number of patients requiring inotropic support in the group with EF $\leq 45\%$ may require a larger patient population to discriminate between duration of bypass and the need for inotropic support. Although not proven, modification of these preoperative and intraoperative risk factors with additional preoperative medical therapy (improved EF and reduced cardiac enlargement) and expeditious surgical intervention (shorter bypass and ischemic times) may improve short-term outcome and reduce the need for inotropic therapy.

The baseline and postcontrast LVEDP measurements were marginally predictive of short-term outcome, i.e., a higher LVEDP was associated with worse outcome. The change in LVEDP was not an independent risk factor for short-term outcome. Although an acute increase in LVEDP is a sensitive marker of myocardial ischemia, the cause and significance of preoperative radiographic contrast-induced increases in LVEDP after ventriculography are controversial. The contrast medium may have a direct myocardial depressant effect because of its high so-dium content (19,20). Ionized calcium levels in blood are transiently depressed after dye injection (owing to chelation) and the addition of calcium to the contrast medium before injection has prevented the

myocardial depression (21). Wolfe et al. (22) found no relationship between the increase in LVEDP after ventriculography and the severity of either coronary artery disease or indexes of systolic left ventricular dysfunction (EF, cardiac index, dP/dt, and left ventricular end-systolic volume index) in 81 consecutive patients undergoing left ventriculography and selective coronary angiography. They concluded that the increase in LVEDP results only from contrast injection and is unrelated to any preexisting ventricular dysfunction. Accordingly, we would agree that contrast-induced change in LVEDP did not independently have any predictive power in left ventricular function after coronary artery bypass grafting except when combined with WMA in patients with EF ≥ 55%.

Do WMA in patients with good left ventricular function (EF \geq 55%) indicate an increased risk for inotropic support and an increased likelihood of a worse short-term outcome? Mangano (8) showed that both decreased preoperative EF and preoperative segmental WMA predicted more severely depressed left and right ventricular function postoperatively in patients undergoing coronary artery bypass surgery. Leung et al. (15) found that postoperative WMA as demonstrated by transesophageal echocardiography was the most reliable predictor of operative outcome. Six of 18 patients with WMA postoperatively had an adverse outcome, defined as myocardial infarction, severe ventricular dysfunction requiring inotropic therapy, or cardiac death, whereas none of the 32 patients without postoperative WMA had an adverse outcome. In our study, the presence of preoperative WMA was not an independent predictor of short- or long-term outcome. However, when WMA were combined with contrast-induced changes in LVEDP of ≥10 mm Hg in patients with good ventricular function (EF \geq 55%), these combined measurements predicted a greater likelihood that postoperative inotropic support would be required, similar to patients with poor ventricular function and low EF (< 55%).

Does the administration of inotropes intraoperatively influence long-term outcome? Although inotropic drugs are absolutely necessary to restore peripheral perfusion in patients with low cardiac output syndrome, inotropes are probably started "prophylactically" in many patients with a marginally acceptable cardiac index without definite signs of low peripheral perfusion. Is this a cause for concern? Oral β_1 receptor stimulants and oral phosphodiesterase-III inhibitors produce symptomatic improvement in patients with chronic heart failure, but worsen outcome by increasing mortality (23,24). In a recent metaanalysis of 21 randomized trials of oral β -adrenergic

agents and phosphodiesterase inhibitors in patients with chronic heart failure, a highly significant increase in overall mortality was found in patients treated with inotropes compared with patients who were randomly assigned to placebo (25). Intermittent intravenous administration of dobutamine in outpatients with chronic heart failure provides sustained improvement in symptoms, but also worsens overall survival (26). The administration of inotropes in acute cardiac failure improves cardiac function, but delays the nadir of depression in left ventricular function by several hours from its usual occurrence immediately after surgery (1). In our study, the clinical decision to administer inotropic drugs appeared to have only marginal significance in relation to long-term adverse outcome after myocardial revascularization. Thus, we believe that the need for inotropic drug support only indicates depressed postoperative ventricular function (the true primary cause of worse long-term outcome), and that the use of inotropic drugs per se does not influence outcome in this population. However, further prospective studies in larger patient populations are needed to answer these questions concerning inotropic drug therapy in cardiac surgery.

Modifying factors related to worse long-term morbidity included the preoperative NYHA symptom score and the duration of cardiopulmonary bypass. Modification of these risks with improved medical and surgical therapy may improve outcome. However, there were an insufficient number of deaths in our study to identify those factors related to mortality. Larger studies relating selected preoperative measurements, intraoperative monitoring techniques, different pharmacologic therapy of ischemia, cardioplegia techniques, and various inotropic drugs to perioperative morbidity and mortality are needed to reduce further the operative risks in coronary artery bypass surgery.

In summary, EF remained the most robust preoperative predictor of the need for postoperative inotropic support and an adverse short-term outcome. Additional, less predictive factors included age, female sex, and an enlarged heart. The intraoperative factors (prolonged pump time and prolonged ischemic time) also correlated with the need for inotropic drug support. Although in unselected patients the presence of WMA or a change in LVEDP (after contrast injection) did not predict the need for postoperative inotropic support, when these factors were combined with preoperative EF, patients could be stratified into groups with low and high likelihood of requiring postoperative inotropic drug support. A worse outcome at 36 mo postoperatively (using NYHA symptom classification scores) was associated

with higher preoperative NYHA scores, older age, female sex, and prolonged duration of cardiopulmonary bypass. The need for intravenous inotropic drug support was of only marginal significance in predicting adverse long-term outcome. This apparent difference between acute and chronic heart failure relating the effects of inotropic stimulation to long-term outcome deserves further study.

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Effects of Altered Pao₂ and Paco₂ on Left Ventricular Function and Coronary Hemodynamics in Sheep

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LEHOT J-J, LEONE BJ, FOËX P. Effects of altered Pao_2 and $Paco_2$ on left ventricular function and coronary hemodynamics in sheep. Anesth Analg 1991;72:737–43.

The effects of acute changes in arterial carbon dioxide and oxygen tension, produced by altering the inspired gas mixtures while maintaining constant-volume intermittent positive pressure ventilation, on global function, regional left ventricular function, and coronary hemodynamics were studied in eight sheep during halothane anesthesia. Hypercapnia (PacO2, 73.5 \pm 2.3 mm Hg, mean \pm SD) increased heart rate, stroke volume, and cardiac output but decreased systolic shortening in the base of the left ventricle. Hypocapnia (PaO2, 24 \pm 1.5 mm Hg) decreased cardiac output and coronary flow below levels seen with hypercapnia but

not below levels seen with normocapnia. Systolic shortening decreased in both apical and basal regions, and left ventricular relaxation was impaired as evidenced by a reduction of the nadir of LV dP/dt. Hypoxemia (Pao₂, 39 \pm 1.5 mm Hg) elicited a hyperdynamic response of the circulation, increased coronary blood flow, and exhausted the coronary flow reserve. Neither changes in Paco₂ nor changes in Pao₂ caused postsystolic shortening, although hypercapnia caused nonuniformity of contraction in the left ventricle. Thus, marked alterations in oxygen and carbon dioxide tensions do not cause left ventricular dysfunction, even though moderate hypoxia reduces the coronary flow reserve.

Key Words: HEART, MYOCARDIAL FUNCTION AND BLOOD FLOW—effects of Po₂ and Pco₂.

The effects of acute hypoxemia and changes in arterial carbon dioxide tension (Paco₂) on global hemodynamics and coronary blood flow have been extensively studied (1–10). However, their effects on coronary flow reserve have not been elucidated. Although the effects of myocardial ischemia on left ventricular (LV) relaxation have been described (11), the effects of hypoxemia and changes in Paco₂ have not been previously investigated. As early relaxation may be altered by anesthesia (12) and by drug interactions (13-15), we wondered whether global and regional relaxation abnormalities may also develop when the "milieu interieur" is altered by changes in carbon dioxide tension or on the occasion of moderate hypoxemia. Should abnormal patterns of contraction and relaxation develop under the influence of changes in Paco2, they would be classified, in echocardiographic studies, as "new wall motion abnormalities" and wrongly attributed to ischemia. In

addition, this study was designed to determine the effects of arterial hypoxemia, hypocarbia, and hypercarbia on the coronary flow reserve.

Methods

In eight sheep, weighing between 28 and 36.5 kg, premedicated with intramuscular morphine sulfate (0.3 mg/kg), anesthesia was induced with 15 mg/kg thiopental and maintained, after endotracheal intubation, with 1.0%-1.2% halothane in a mixture of oxygen (50%) and nitrogen. Constant-volume intermittent positive pressure ventilation was instituted (Penlon, Oxford Ventilator) at a rate of 12 breaths/min with a tidal volume of 40 mL/kg. Three to five percent CO₂ was added to maintain the end-expiratory CO₂ at 5%-5.3% (infrared CO₂ analyzer). The inspired oxygen concentration was measured with a paramagnetic oxygen analyzer sampling from the inspiratory limb of the anesthetic circuit. Temperature, measured at the midesophagus, was maintained between 37 and 38°C by a heating element incorporated into the operating table. Airway pressure was measured through a wide-bore needle inserted into the endotracheal tube and connected to a Statham P23De pressure transducer.

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An intravenous catheter threaded into the inferior vena cava through a femoral vein was used to administer 0.9% saline at a constant rate of 5 mL·kg⁻¹·h⁻¹. The left common carotid artery was exposed and a rigid 8F polyethylene catheter was advanced to within 1 cm of the aortic valve. This catheter was used to measure aortic pressure (Statham P23De pressure transducer) and to withdraw blood samples for blood gas analysis. Lead II of the electrocardiogram was monitored.

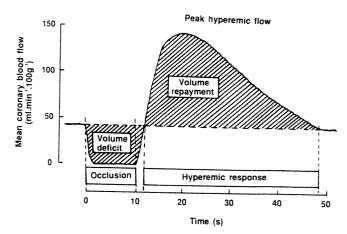
A left thoracotomy was performed; the fourth, fifth, and sixth ribs excised; and the heart suspended in a pericardial cradle. The fat pad around the root of the aorta was removed and an electromagnetic flow transducer (SEM 275, SE Laboratories, Feltham, U.K.) of appropriate size was placed around the vessel. A rigid 8F Portex cannula cut to 10 cm was inserted into the left ventricle through a small incision in the apex and used to measure LV pressure (Druck pressure transducer, Groby, U.K.). A catheter was inserted into the pulmonary artery through the outflow tract of the right ventricle and used to inject indocyanine green to determine cardiac output and thus calibrate the electromagnetic flowmeter in vivo. The left circumflex coronary artery was dissected and coronary flow was measured with an electromagnetic flow transducer (SEM 275, SE Laboratories, Feltham, U.K.). A 00 Dacron suture was placed distal to the flow probe and used for intermittent occlusion of the left circumflex coronary artery to obtain occluded zero flow calibration and to impose brief occlusions (10 s) to evaluate the hyperemic response of the coronary circulation.

Two pairs of piezoelectric crystals were introduced into the subendocardium for measurement of segment length by sonomicrometry (16,17). One pair was placed in the basal region of the left ventricle (supplied by the left circumflex coronary artery) and the other in the near apical region (supplied by the left anterior descending coronary artery).

After operation the animals were allowed to stabilize for 1 h while being ventilated with 1.2% inspired halothane to achieve cardiovascular stability. During this period dextran (molecular weight, 70,000) was added to maintain LV end-diastolic pressure greater than 5 mm Hg, and 4.2% bicarbonate solution was administered to maintain arterial pH between 7.35 and 7.45.

Experimental Design

Each experiment started with a study of the effects of altered Paco₂. For this part of the study, CO₂ was added to the inspired gas mixture (50% oxygen,



<u>Figure 1</u>. Hyperemic response to a brief period (10 s) of coronary occlusion showing how peak coronary flow, duration of hyperemic response, volume deficit, and volume repayment were determined.

balance nitrogen) in amounts sufficient to establish end-expired CO₂ levels of 5.1% (baseline 1), 2.5% (hypocapnia), 8.5% (hypercapnia), and 5.1% (baseline 2). Recordings and arterial blood samples were obtained after 20 min of exposure to each new gas mixture. The order of hypocapnia and hypercapnia was established at random. After returning to normocapnia, recordings were obtained after 40 min (baseline 2), and the study of the effects of hypoxia was commenced. Whereas the end-expiratory concentration of CO2 was maintained at 5.1%, the inspired concentration of oxygen was reduced from 50% to 15% and 8% by altering the oxygen-nitrogen balance. Recordings and blood samples were obtained after 20 min of exposure to each new gas mixture. Throughout the study, tidal volume and respiratory rate were maintained constant.

Measurements and Calculations

The aortic blood flow signal was integrated electronically to obtain stroke volume, the latter being calibrated in vivo by the indocyanine green dilution method. The LV pressure signal was differentiated electronically to yield LV dP/dt. Similarly, the aortic flow signal was differentiated to yield aortic blood acceleration.

During each stage of the experiment, occlusive zero flow values for coronary blood flow were obtained by means of an occlusive snare. Occlusion was maintained for exactly 10 s, and the subsequent hyperemic response was recorded (Figure 1) and analyzed in terms of peak hyperemic flow and payback of the flow debt using the method of Buckberg et al. (18); i.e., calculated as the ratio of volume repay-

ment over volume deficit, expressed as percent. Coronary blood flow was calibrated after the end of the experiment by measuring the deflection produced by injection of 5-mL aliquots of blood into the coronary artery. At the end of this procedure, blue ink was injected into the coronary artery and the area supplied by the left circumflex coronary artery was dissected following the subendocardial demarcation of the colored area. After weighing the excised area, coronary flow was expressed in milliliters per 100 g of tissue per minute.

For the purpose of regional function analysis, end-diastole was defined as the time of onset of the increase in LV dP/dt and end-systole as the time at which the aortic flow signal returned to zero. Systolic shortening was calculated as the difference between end-diastolic and end-systolic length and expressed as a percentage of end-diastolic length. Postsystolic shortening was calculated as the difference between end-systolic length and the minimum length during diastole and expressed as percentage of total shortening.

Heart rate was calculated from the RR interval of the electrocardiogram. Coronary perfusion pressure was calculated as aortic diastolic pressure minus LV end-diastolic pressure.

The time constant of isovolumic relaxation (T relax) was calculated by regression analysis of the logarithm of instantaneous pressure against time for the period from peak negative LV dP/dt to the time LV pressure was 10 mm Hg above LV end-diastolic pressure (19). Conditions defined by Martin and coworkers (20) for measurement of LV dP/dt and T relax were fulfilled.

All signals were recorded on an ink-jet recorder (Mingograf 81, Elema Schonander, Stockholm, Sweden). Blood gas tensions and pH were measured with an ABL2 automatic blood gas analyzer (Radiometer, Copenhagen, Denmark). Hemodynamic data were manually digitized and statistical analysis was by two-way analysis of variance followed by Duncan's multiple range test utilizing a commercially available statistical analysis program (SAS Institute, Inc., Cary, N.C.). Linear regression (least-squares method) was used when appropriate. P < 0.05 was considered to be significant. Results are expressed as mean \pm SEM.

Results

Changes in Paco₂

As no attempt was made to keep pH constant, pH changed with the change in Paco₂. However, Pao₂ remained constant during changes in Pco₂.

Global cardiac function. When compared with baseline data, hypocapnia did not modify global cardiac function, except for a 24% reduction in negative LV dP/dt_{max} (Table 1). Hypercapnia significantly increased heart rate, stroke volume, cardiac output, and aortic blood acceleration, whereas it reduced systemic vascular resistance.

When compared with hypercapnia, hypocapnia resulted in slower heart rate and lower stroke volume and cardiac output, whereas vascular resistance and time constant of relaxation increased.

Regional function. Both hypocapnia and hypercapnia decreased systolic shortening in the basal segment, whereas only hypocapnia decreased systolic shortening in the apical region (Table 2). Comparison of the segments showed that systolic shortening was substantially greater in the apical than in the basal region during hypercapnia (P < 0.05; Figure 2) but not during normocapnia or hypocapnia. Postsystolic shortening was unchanged in both apical and basal segments.

Coronary hemodynamics. The only significant change was a reduction in coronary blood flow when hypocapnia was compared with hypercapnia (Table 2). Also, hypercapnia reduced coronary resistance both before and during peak hyperemia.

Нурохетіа

Alterations in Pao_2 were not associated with any change in pHa or $Paco_2$. The first stage of hypoxemia (Pao_2 , 68.3 ± 2.3 mm Hg) did not cause any significant change in global function, regional function, and coronary hemodynamics. However, the second stage had marked stimulatory effects on the circulation reflected in increases in heart rate, cardiac output, and peak aortic blood acceleration.

Global function. Heart rate, cardiac output, LV enddiastolic pressure, and peak aortic blood acceleration all increased significantly during hypoxemia, whereas systemic vascular resistance decreased (Table 1).

Regional function. Hypoxemia did not affect enddiastolic length or segmental shortening. Postsystolic shortening was unchanged in both apical and basal segments (Table 2).

Coronary circulation. Coronary perfusion pressure decreased significantly, but coronary blood flow increased by 151% in association with a significant

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Table 1. Hemodynamic Responses to Acute Changes in Paco₂ and Pao₂

	Baseline 1	Hypercapnia	Hypocapnia	Baseline 2	$F_{10_2} = 0.15$	$F_{1O_2} = 0.08$
Arterial blood gases						
Pao ₂ (mm Hg)	236.3 ± 15.8	237.0 ± 20.3	269.3 ± 18.0	252.8 ± 15.0	$68.3 \pm 2.3^{\circ}$	$39.0 \pm 1.5^{\circ}$
Paco ₂ (mm Hg)	39.0 ± 1.5	73.5 ± 2.3^{b}	24.0 ± 1.5^{b}	39.0 ± 0.8	37.5 ± 0.8	40.5 ± 0.8
pHa (U)	7.43 ± 0.01	7.22 ± 0.02^{b}	$7.61 \pm 0.03^{b,c}$	7.42 ± 0.01	7.44 ± 0.02	7.42 ± 0.01
Global hemodynamics						
Heart rate (beats/min)	109 ± 5	125 ± 4^{b}	110 ± 3^{c}	110 ± 6	118 ± 5	137 ± 15^d
Mean arterial pressure (mm Hg)	64 ± 3	58 ± 2	57 ± 4	63 ± 4	60 ± 4	56 ± 5
LV end-diastolic pressure (mm Hg)	7.2 ± 1.1	6.9 ± 1.3	8.1 ± 0.9	10.0 ± 1.4	9.0 ± 1.3	13.4 ± 1.0^d
Stroke volume (mL)	23.3 ± 2.9	27.4 ± 3.3^{b}	$21.4 \pm 2.6^{\circ}$	22.9 ± 3.0	23.1 ± 3.4	24.2 ± 2.1
Cardiac output (mL/min)	2557 ± 356	3436 ± 403^{b}	$2771 \pm 301^{\circ}$	2511 ± 342	2780 ± 457	3196 ± 257°
Total peripheral resistance (U)	24.0 ± 5.0	$15.8 \pm 3.0^{\circ}$	24.7 ± 7.1^{f}	25.9 ± 7.1	23.2 ± 6.5	14.5 ± 1.4^d
Positive LV dP/dt _{max} (mm Hg/s)	962 ± 68	1019 ± 33	837 ± 94	806 ± 73	850 ± 116	1037 ± 174
Peak aortic blood acceleration (mL/s2)	4334 ± 641	$5513 \pm 707^{\circ}$	$3791 \pm 708^{\circ}$	4172 ± 756	4539 ± 966	6196 ± 1025^d
Negative LV dP/dt _{max} (mm Hg/s)	937 ± 82	1000 ± 63	$775 \pm 108^{c,e}$	906 ± 94	862 ± 103	925 ± 151
T relax (ms)	36.8 ± 3.6	33.3 ± 2.0	41.9 ± 3.5^f	41.9 ± 2.4	39.7 ± 1.6	37.4 ± 1.5

Values are expressed as mean \pm sem. n=8. Baselines at Fro₂ = 0.5.

decrease in coronary vascular resistance (Table 2). Resting and peak hyperemic coronary flows were almost identical (Figure 3). Repayment of the volume deficit was reduced to 13% of baseline levels by hypoxemia.

Discussion

Changes in Paco₂

The hemodynamic effects of changes in Paco₂ are the result of the direct effects of carbon dioxide on the myocardium and the peripheral vasculature and the effects on the sympathetic nervous system. Hypercapnia is known to decrease contractility in isolated heart muscle preparations (21,22), to cause peripheral vasodilatation, and, unless β -adrenoceptor blockers have been administered, to cause a hyperdynamic response of the circulation. The latter is due to sympathetic overactivity and increases catecholamine release (23,24). Hypercapnia also causes coronary vasodilatation (10,25,26). Hypocapnia has effects opposite to those of hypercapnia. Halothane anesthesia may be expected to cause myocardial depression and to blunt the response of the sympathetic system to hypercapnia (27).

In the present study, hypercapnia induced a hyperdynamic response of the circulation in agreement with previous findings in humans (5) and dogs (28). In the face of the hyperdynamic response of the circulation, regional function in the basal region of

the left ventricle decreased significantly. This suggests that nonuniformity of LV function develops because of alterations in the cellular environment. Either the basal region is more sensitive to the direct depression of hypercapnic acidosis, or it is less sensitive to sympathetic stimulation. Differences in regional function have been previously described in dogs (29,30) but not in sheep. Such differences do not appear to be present in sheep under "unstressed" conditions, at least under anesthesia.

The decrease in coronary vascular resistance seen in the present study with increases in Paco₂ was the same as that reported in conscious sheep exposed to a similar degree of hypercapnia (31), indicating that halothane does not alter the coronary vascular responsiveness during hypercapnia. Buckberg and coworkers (18) showed that the ratio between subendocardial and subepicardial coronary flow remained normal until the percentage payback after coronary occlusion was less than 150%. As the percent payback did not decrease below this level in the present study, the subendocardium remained normally perfused and abnormal patterns of wall motion were not observed.

In keeping with previous studies, hypocapnic alkalosis did not alter global cardiac function (25,32). Systolic shortening in the basal segment decreased significantly when compared with control. Similarly systolic shortening in the apical region decreased when compared with hypercapnia. This is at variance with the slight increases observed by Coetzee et al.

 $^{^{\}bullet}P < 0.01$ versus baseline 2.

 $[^]bP < 0.01$ versus baseline 1.

 $^{^{}c}P < 0.01$ versus hypercapnia.

 $[^]dP < 0.05$ versus baseline 2.

 $^{^{\}circ}P < 0.05$ versus baseline 1.

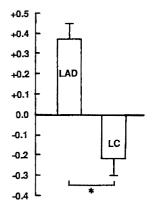
fP < 0.05 versus hypercapnia.

Table 2. Regional Function and Coronary Dynamics in Response to Acute Changes in Paco2 and Pao2

	Baseline 1	Hypercapnia	Hypocapnia	Baseline 2	$F_{10_2} = 15\%$	$Fro_2 = 8\%$
Regional function						
Apical segment						
EDL (mm)	13.0 ± 0.8	13.3 ± 0.8	$12.6 \pm 0.9^{a,b}$	13.2 ± 0.8	13.0 ± 0.9	13.1 ± 0.7
Percent shortening	26.5 ± 2.4	28.4 ± 1.4	$23.8 \pm 2.2^{\circ}$	24.7 ± 2.8	23.8 ± 2.8	25.3 ± 2.7
Percent PSS	0.0 ± 0.0	0.3 ± 0.3	1.2 ± 1.2	2.3 ± 2.3	1.9 ± 1.6	1.6 ± 0.8
Basal segment						
EDL (mm)	13.1 ± 1.2	12.8 ± 1.1	12.7 ± 1.0	13.1 ± 1.1	12.9 ± 1.1	13.5 ± 1.0
Percent shortening	24.9 ± 2.4	$23.3 \pm 2.2^{\circ}$	23.5 ± 2.5°	23.0 ± 2.3	22.5 ± 2.5	23.3 ± 2.4
Percent PSS	5.0 ± 1.7	3.2 ± 1.3	6.2 ± 1.8	6.5 ± 0.7	4.9 ± 1.8	1.2 ± 0.8
Coronary dynamics						
Coronary perfusion pressure (mm Hg)	51 ± 4	44 ± 2	45 ± 4	47 ± 4	45 ± 4	$34 \pm 4^{\circ}$
Coronary flow (mL·min ⁻¹ ·100 g ⁻¹)	112 ± 22	138 ± 22	92 ± 14^{c}	94 ± 11	124 ± 26	238 ± 50^{4}
CVR (U/100 g)	555 ± 90	$363 \pm 50^{\circ}$	545 ± 70	546 ± 70	446 ± 70	248 ± 90 ⁴
Peak hyperemic coronary flow (mL·mm ⁻¹ ·100 g ⁻¹)	206 ± 15	231 ± 40	201 ± 23	194 ± 22	208 ± 38	236 ± 64
CVR at peak hyperemia (U/100 g)	254 ± 20	$212 \pm 20^{\circ}$	238 ± 20	263 ± 30	253 ± 40	253 ± 90
Hyperemic response (mL)	33 ± 5	41 ± 11	41 ± 11	33 ± 6	36 ± 14	7 ± 7
Duration of hyperemia (s)	40 ± 4	49 ± 6	38 ± 5	34 ± 4	35 ± 8	9 ± 7^d
Percent payback of flow debt	228 ± 49	190 ± 35	293 ± 57	213 ± 37	187 ± 47	13 ± 12^d

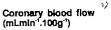
EDL, end-diastolic length; PSS, postsystolic shortening; CVR, coronary vascular resistance. Other symbols as in Table 1. Values are expressed as mean \pm sem. n=8.

Change in systolic shortening (mm)



<u>Figure 2</u>. Regional differences in responses to hypercapnia between apical and basal segments.

(32) in a dog model and may represent a species difference. A significant reduction in negative LV dP/dt_{max} occurred in the absence of other changes in global hemodynamics. This suggests that hypocapnia decreased LV relaxation. Furthermore, the time constant of relaxation, T relax, was prolonged significantly, in contrast to what was seen during hypercapnia. The difference in relaxation between hypercapnia and hypocapnia may be a reflection of the increase in sympathetic activity with hypercapnia as catecholamines enhance relaxation (33). The relative stability of coronary blood flow



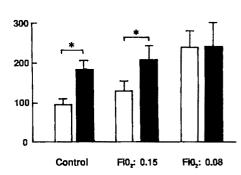


Figure 3. Differences in blood flow in the left circumflex coronary artery between basal conditions (open columns) and peak hyperemia (closed columns). At $Fio_2 = 0.08$, the hyperemic and resting flows are identical. Values are mean \pm sem. *P < 0.05.

during hypocapnic alkalosis is in keeping with the observations of Coetzee et al. (32), although other studies have found a small reduction of coronary flow (23,34). When compared with hypercapnia, however, coronary flow was significantly reduced by hypocapnia and a linear relationship between $Paco_2$ and coronary flow was observed (P < 0.001) as previously reported by Foëx et al. (9). The reduction of coronary flow was not associated with a decrease in the coronary flow reserve as evidenced by normal peak hyperemic flow and unaltered duration of hyperemia. Hypercapnia induced nonuniformity of

 $^{^{\}bullet}P < 0.05$ versus baseline 1.

 $^{^{}b}P < 0.01$ versus hypercapnia.

^cP < 0.05 versus hypercapnia.

 $^{^{4}}P < 0.05$ versus baseline 2.

ventricular contraction (Figure 2), but did not cause any postsystolic shortening. Similarly, hypocapnia delayed relaxation but did not cause paradoxical wall motion in the normal myocardium. Thus, alterations in arterial carbon dioxide tension associated with marked alterations in arterial pH do not cause dyssynchrony of contraction in the left ventricle, although they may reveal non-uniformity of contraction.

Hypoxemia

Although mild hypoxemia did not alter the circulation, more severe hypoxemia caused marked increases in heart rate and cardiac output. Left ventricular relaxation was not altered by hypoxemia. This is in sharp contrast to the impairment in LV relaxation in myocardial ischemia (11,35). In isolated heart muscle, hypoxemia prolongs isovolumic relaxation (36), and, in the intact heart, acute reductions in coronary blood flow are associated with delayed relaxation (37). This effect may not be specific for oxygen deprivation but results from the loss of the contribution of coronary flow to relaxation, as coronary flow during isovolumic relaxation is thought to facilitate relaxation (38,39). However, in the face of hypoxemia, the effect of compromised oxygenation (if present at all) is compensated by the increase in coronary blood flow and by the lusitropic effect of sympathetic activation (33). In spite of the reduction in coronary perfusion pressure, coronary blood flow increased and reached levels similar to those observed during peak hyperemia. Thus the 10-s occlusion was followed by a large deficit in payback of the flow debt, which decreased below the critical level suggested by Buckberg and coworkers (18), a level at which a substantial reduction of flow to the subendocardium may be expected. Although an abnormal distribution of flow may have occurred, patterns of regional dysfunction (postsystolic shortening) were not observed, suggesting that oxygen delivery to the subendocardium was still sufficient to sustain normal wall motion.

It may be argued that the effects of hypoxia were influenced by the study of the effects of altered Pco₂ that was carried out immediately before. However, there were no significant differences in hemodynamic values between baseline 1 and baseline 2, suggesting that the study of hypoxia was not invalidated by the effect of CO₂ changes nor by a time-related decay of the preparation.

Finally, it could be argued that the effects of altered CO₂ and oxygen tensions were due essentially to alterations in right ventricular function secondary to

changes in pulmonary vascular resistance. Both hypercapnia and hypoxia increase vascular resistance, although not necessarily pulmonary input impedance (40,41). The increase in resistance should cause a reduction rather than an increase in right ventricular output. In addition, an increase in pulmonary vascular resistance would be expected to impede right ventricular emptying. This, in turn, may impair LV relaxation (38,39). However, we have observed an enhancement and not an impairment of relaxation with hypercapnia, and no change with hypoxia. Thus, the effects of altered blood gases described in this study are likely to be caused by changes in left ventricular function, some of which may be mediated by the sympathetic nervous system. It is unlikely that they are due primarily to changes occurring in the pulmonary circulation and in the right ventricle.

In conclusion, the hemodynamic responses to altered carbon dioxide and oxygen tensions observed in sheep during constant levels of halothane anesthesia are similar to those reported in humans and in dogs. The additional information provided by this study is that changes in Paco₂ may alter coronary vascular resistance but do not influence the coronary reserve, as the hyperemic responses are essentially unchanged. However, hypoxemia reduces the coronary reserve because coronary flow is already elevated and coronary resistance cannot be reduced much further by a short period of ischemia. Because hypoxemia was not severe, patterns of contraction remained normal and relaxation was not impaired. This may be explained by the relaxing effect of both high coronary blood flow and sympathetic activation. Hypocapnia caused a moderate reduction in LV relaxation. Whether this effect is due primarily to hypocapnia or to the reduction in coronary flow cannot be determined. The absence of paradoxical wall motion indicates that even large variations in arterial Pco2 and pH, as well as moderate hypoxemia, are unlikely to cause clinically detectable wall motion abnormalities.

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Circulatory Effects of Verapamil During Normovolemic Hemodilution in Anesthetized Rats

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SHINODA T, SMITH CE, ESTAFANOUS FG, KHAIRALLAH PA. Circulatory effects of verapamil during normovolemic hemodilution in anesthetized rats. Anesth Analg 1991;72:744–50.

Patients who have undergone perioperative normovolemic hemodilution may require calcium channel blockers for the treatment of myocardial ischemia and/or supraventricular tachyarrhythmias. The purpose of this rodent study was to examine the effect of intravenous verapamil on the hyperdynamic circulatory response to acute normovolemic hemodilution (hematocrit 20%). Anesthetized animals were randomly divided into four groups equal in number: (1) controls (no hemodilution, no drug); (2) hemodilution only; (3) verapamil only; and (4) hemodilution followed by verapamil. Cardiac output was recorded using an electromagnetic flow probe. Pre- and afterload tests were performed, the former consisting of rapid infusion of blood adjusted for hematocrit, the latter consisting of an aortic clamp technique. Animals in group 2 had significantly (P <

0.05) greater percent increases in cardiac index, stroke volume index, and dP/dt, and greater percent decreases in mean arterial pressure, systemic vascular resistance, and oxygen delivery than did control animals (group 1). Infusion of verapamil after hemodilution (group 4) did not interfere with the compensatory increases in cardiac index and stroke volume index seen in group 2, nor did it reduce the peak stroke volume index in response to preload stress, although it did reduce resting dP/dt, mean arterial pressure and systemic vascular resistance, and peak cardiac index and "left ventricular developed pressure" after preload and afterload stress, respectively. We conclude that reduced ventricular function after verapamil administration does not interfere with the compensatory increase in stroke volume index after normovolemic hemodilution.

Key Words: BLOOD, HEMODILUTION—verapamil effects. PHARMACOLOGY, CALCIUM BLOCKERS—verapamil.

Anesthesiologists may use acute normovolemic hemodilution during cardiac and general surgery to conserve blood, decrease the risks associated with transfusion of homologous blood, decrease blood viscosity during cardiopulmonary bypass, and improve tissue perfusion to the microcirculation (1,2). Circulatory changes associated with acute normovolemic hemodilution include increased cardiac output (CO) and stroke volume, decreased blood pressure and systemic vascular resistance (SVR), redistribution of blood flow to some tissues, and increased oxygen extraction ratio (3–7). However, conditions that diminish left ventricular function and SVR may affect the compensatory increases in CO and stroke volume elicited by acute reductions in red

Verapamil is a calcium-entry blocker that selectively interferes with the inward calcium movement across cell membranes (15). This may result in decreases in sinus node pacemaker activity, atrioventricular nodal conduction, myocardial contractility, SVR, and blood pressure (16). It is unclear whether verapamil interferes with the normal compensatory response to acute normovolemic hemodilution. This study was designed to investigate the cardiovascular effects of intravenous verapamil therapy during normovolemic hemodilution with hetastarch in rats.

The study has clinical relevance because anesthesiologists may encounter patients who have undergone hemodilution and who require verapamil for the treatment of supraventricular tachyarrhythmias

cell mass and oxygen content of arterial blood (8). For example, cardiac sympathetic denervation (9,10), experimental myocardial infarction (11), and druginduced myocardial depression (12–14) interfere with circulatory responses to normovolemic hemodilution.

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and/or myocardial ischemia in the perioperative setting.

Methods

Experimental Preparation

The protocol was approved by the Cleveland Clinic Foundation Animal Research Committee. Male, Sprague-Dawley rats (age, 12 wk) were anesthetized with 100 mg/kg thiobutabarbital (Inactin) intraperitoneally (17,18). After tracheal cannulation, the lungs were ventilated with room air using a Harvard Rodent Ventilator (model 683) at a rate of 50 breaths/ min. Tidal volume was adjusted according to body weight, and 3 cm H₂O positive end expiratory pressure was applied. Body temperature was maintained at 37°C by appropriate positioning of a heating lamp. The right femoral artery and vein were cannulated using PE-50 catheters. Heart rate (HR) and mean femoral artery pressure (MAP) were recorded continuously. Midsternal thoracotomy allowed placement of an electromagnetic flow probe (internal diameter, 2.5 mm) over the ascending aorta for continuous measurement of aortic blood flow. Ascending aortic flow was considered equivalent to CO, and as such excluded coronary flow. Left ventricular end diastolic pressures (LVEDP) and left ventricular maximal dP/dt were recorded using a PE-50 tip-tapered catheter that had been advanced into the left ventricle from the right carotid artery. Preliminary studies in our laboratory have shown that flowmeter-measured aortic blood flow was not affected by the presence of the PE-50 catheter inside the aorta. Heparin, 500 U/kg, was given intravenously for anticoagulation.

Acute normovolemic hemodilution was induced by the simultaneous withdrawal of blood from the right femoral artery and infusion of a similar volume of warmed, isotonic 6% hetastarch dissolved in 0.9% saline (HESPAN) into the right femoral vein at a rate of 1.94 mL/min for 7 min. A volume equivalent to 3.8% of body weight was exchanged to reduce the hematocrit from approximately 50% to 20% (19). Previous experiments have shown that the hematocrit, reduced in this way, stabilizes at its lower level within 15 min, and remains at that level for at least 2 h afterward (20).

Experimental Protocol

Animals were randomly divided into four groups of six animals according to the experimental design as follows:

- 1. control (no hemodilution, saline infusion)
- 2. hemodilution alone (hemodilution, saline infusion)
- 3. verapamil alone (no hemodilution, verapamil infusion)
- 4. both hemodilution and verapamil.

Verapamil, $50 \, \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ diluted in saline, or saline alone was administered intravenously at a rate of $0.6 \, \text{mL/h}$ for $0.75 \, \text{h}$ after hemodilution. This dose of verapamil was chosen to reduce MAP by 30% (21).

Resting Cardiovascular Measurements

Animals rested for 60 min after thoracotomy and surgical instrumentation. Baseline hemodynamic measurements were recorded on a Gould 4 channel monitor (model 2400, Gould, Inc., Cleveland, Ohio) using Spectramed disposable pressure transducers (Spectramed Inc., Oxnard, Calif.). Measured frequency response values were 10-43 Hz. The low upper end frequency response of the catheter and transducer system used to measure left ventricular pressures was due to a change in capacitance of the front end filter of the amplifier, which affected the overall frequency response of one channel. Because this filtering of one channel occurred for all treatment groups, intergroup comparisons were valid. Arterial blood was sampled for measurement of hematocrit (International Microcapillary Centrifuge, model MB), hemoglobin, carbon dioxide and oxygen tensions, base excess, oxygen saturation, and oxygen content (ABL3 Radiometer, Copenhagen, Denmark). The oxygen saturation curve was calibrated using the P50 of rats (19). A second set of hemodynamic measurements was recorded 30 min after initiation of hemodilution. A third set of hemodynamic measurements was made and a second arterial blood sample obtained 30 min after intravenous drug or saline administration (60 min after hemodilution). The following indices were calculated: cardiac index (CI) = CO/ body weight; stroke volume index (SVI) = CI/HR; oxygen delivery = CI × oxygen content; SVR = MAP/CI. The small magnitude of error introduced by ignoring central venous pressure in the estimate of SVR was unlikely to have influenced the results to any great extent (22).

Myocardial Performance in Response to Stress

After the third set of hemodynamic measurements (60 min after hemodilution) and during intravenous

<u>Table 1</u>. Baseline Values (B) and Percent Changes From These Values 30 and 60 Minutes After Hemodilution (T_1 and T_2 , respectively)

	Control	Hemodilution	Verapamil	Both
Body weight				, <u>, , , , , , , , , , , , , , , , , , </u>
B (g)	383 ± 7	382 ± 2	390 ± 4	392 ± 7
Heart rate				
B (beats/min)	374 ± 13	370 ± 8	376 ± 9	376 ± 1
T ₁ (%)	-0.1 ± 0.6	0.4 ± 3	3.2 ± 1.8	0.1 ± 2.2
T ₂ (%)	-0.4 ± 1	0.7 ± 3	-13.2 ± 1.9^d	$-21.4 \pm 3.6^{b,c}$
LVEDP (mm Hg)	3.6 ± 0.1	3.6 ± 0.2	3.3 ± 0.2	3.2 ± 0.4
T ₁ (%)	-11 ± 2	10 ± 8	-6 ± 8	13 ± 7
T ₂ (%)	-14 ± 7	10 ± 6	38 ± 14^d	$84 \pm 17^{b,c}$
dP/dt (mm Hg)	67 ± 3	63 ± 2	64 ± 1	66 ± 3
T ₁ (%)	-6 ± 1	13 ± 3 ^a	-1 ± 1	11 ± 3^b
T_2 (%)	-10 ± 2	8 ± 3*	-36 ± 3^{d}	$-26 \pm 3^{b,c}$
Oxygen delivery				
B (mL·min ⁻¹ ·kg ⁻¹)	55.7 ± 2.3	54.5 ± 3.2	53.9 ± 2.9	54.4 ± 2.1
T ₂ (%)	-3 ± 2	$\cdot \qquad -39\pm3^a$	9 ± 4^d	-41 ± 4^b

LVEDP, left ventricular end diastolic pressure.

drug or saline infusion, myocardial stress tests were performed as described by Fletcher et al. (23). For the pressure load (afterload), test, the ascending aorta was occluded for 3 s with a preplaced snare for the calculation of left ventricular developed pressure (left ventricular developed pressure = peak left ventricular systolic pressure — LVEDP). Ten minutes after the pressure load test, when cardiovascular parameters had returned to prestress baseline, the volume load (preload) test was initiated. Warmed, diluted blood adjusted to the recipient animal's hematocrit was infused into the right femoral vein at a rate of 15.3 mL/min. This procedure allowed determination of CI and SVI at increments of LVEDP in order to ascertain their peak values (23).

Statistical Analysis

Between-group statistical comparisons were done with a one-way analysis of variance followed by the Fisher least significant difference method. A P value less than 0.05 was considered to be statistically significant. The results are expressed as mean \pm standard error of the mean (SEM).

Results

Cardiovascular parameters after hemodilution (T_1) and verapamil (T_2) are shown in Table 1 and Figures

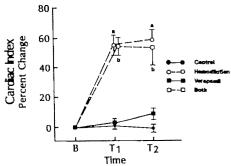


Figure 1. Change in CI from baseline (B) 30 min after hemodilution (Γ_1) and 60 min after hemodilution (30 min after infusion of verapamil, T_2). a: P < 0.05, hemodilution versus control; b: P < 0.05, both versus verapamil.

1--4. Arterial blood measurements at baseline and T_2 are shown in Table 2. Arterial oxyhemoglobin saturation exceeded 95% throughout the study. There were no significant intergroup differences at baseline. There were no significant changes in hemodynamics, acid-base status, oxygenation, and hematocrit during the experiment in control animals, indicating the stability of the preparation.

Compared with controls, animals in group 2 (hemodilution only) had significant decreases in MAP, SVR, and oxygen delivery, and significant increases in CI, SVI, dP/dt, LVEDP, peak CI, and peak SVI. Heart rate and left ventricular developed pressure were not affected by hemodilution. Results of myocardial stress tests are summarized in Table 3.

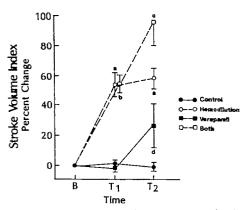
Infusion of verapamil in nonhemodiluted animals

Values are expressed as mean ± SEM.

 $^{^{4}}P < 0.05$, hemodilution versus control.

 $^{^{}b}P < 0.05$, both versus verapamil.

 $^{^{}c}P < 0.05$, both versus hemodilution. $^{d}P < 0.05$, verapamil versus control.



<u>Figure 2</u>. Change in SVI from baseline (B) 30 min after hemodilution (T_1) and 60 min after hemodilution (30 min after infusion of verapamil, T_2). a: P < 0.05, hemodilution versus control; b: P < 0.05, both versus verapamil; c: P < 0.05, both versus hemodilution; and d: P < 0.05, verapamil versus control.

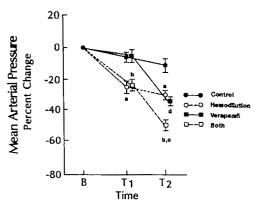
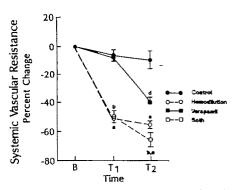


Figure 3. Change in mean arterial pressure from baseline (B) 30 min after hemodilution (T_1) and 60 min after hemodilution (30 min after infusion of verapamil, T_2). a: P < 0.05, hemodilution versus control; b: P < 0.05, both versus verapamil; c: P < 0.05, both versus hemodilution; and d: P < 0.05, verapamil versus control.

(group 3) resulted in significant decreases in HR, dP/dt, MAP, SVR, left ventricular developed pressure, and peak CI, and significant increases in SVI and LVEDP compared with controls. Cardiac index and oxygen delivery were not altered.

Compared with groups 1 and 3 (control and verapamil only groups), infusion of verapamil after hemodilution in group 4 was associated with significantly lower HR, MAP, SVR, and oxygen delivery, and significantly higher CI and SVI. Group 4 animals had significantly higher dP/dt and peak SVI compared with group 3, and they had lower dP/dt, peak CI, and left ventricular developed pressure compared with controls.

Compared with group 2, infusion of verapamil in group 4 resulted in significant decreases in HR, MAP, dP/dt, SVR, left ventricular developed pressure, and peak CI, and significant increases in SVI and LVEDP.



<u>Figure 4</u>. Change in systemic vascular resistance from baseline (B) 30 min after hemodilution (T_1) and 60 min after hemodilution (30 min after infusion of verapamil, T_2). a: P < 0.05, hemodilution versus control; b: P < 0.05, both versus verapamil; c: P < 0.05, both versus hemodilution; and d: P < 0.05, verapamil versus control.

Cardiac index, oxygen delivery, and peak SVI were similar between these two groups.

Discussion

Normal cardiovascular responses to acute normovolemic hemodilution include increases in CO, stroke volume, and organ blood flow to meet tissue oxygen demands (1,24,25). Despite the lowered oxygen content of the diluted arterial blood, experimental data in both humans (26,27) and animals (6,7,28) indicate that acute normovolemic hemodilution is well tolerated under resting conditions. This is evidenced by improved organ perfusion and tissue oxygenation owing to the beneficial rheological properties of diluted blood and the increased cardiac output (7). The increased CI after hemodilution in the present study was not as great as the decrease in oxygen content of the diluted blood, so that oxygen delivery was reduced regardless of calcium channel blockade. It is possible that other intrinsic factors, such as alterations in oxygen extraction mechanisms (4) and/or redistribution of blood flow to organs such as the heart and brain (22), play important compensatory roles in the maintenance of tissue oxygenation during hemodilution. Indeed, Scherer et al. (29) showed that gradual dextran hemodilution to hematocrits as low as 15%-20% resulted in significant increases in the oxygen extraction ratio in normoxic dogs treated with verapamil.

The results of the present study demonstrated that administration of verapamil after hemodilution does not attenuate the compensatory increases in CI and SVI despite significant reductions in dP/dt, HR, SVR, and MAP. Similar lack of attenuation of SVI has been reported in verapamil-treated hemodiluted dogs, al-

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Table 2. Hematocrit, Oxygen Content, and Arterial Blood Gas at Baseline (B) and 30 Minutes After Infusion (T2)

Group	Time	Hematocrit (%)	Oxygen content (mL/dL)	pН	Pco₂ (mm Hg)	Po ₂ (mm Hg)	Base excess (mmol/L)
Control	В '5-	49.3 ± 0.6	27.6 ± 0.8	7.405 ± 0.015	37.3 ± 1.5	104.1 ± 4.2	-0.9 ± 0.4
	T_2	$^{-49.7} \pm 0.5$	27.0 ± 0.7	7.389 ± 0.008	37.4 ± 1.2	104.5 ± 2.6	-1.8 ± 0.4
Hemodilution B	В	51.7 ± 0.4	28.2 ± 0.7	7.391 ± 0.003	36.1 ± 0.6	99.8 ± 1.8	-2.2 ± 0.5
	T_2	$20.4 \pm 0.5^{\circ}$	$10.9 \pm 0.2^{\circ}$	$7.351 \pm 0.005^{\circ}$	36.4 ± 0.9	102.0 ± 3.8	-4.9 ± 0.6^{a}
Verapamil	В	50.7 ± 0.8	28.2 ± 0.7	7.393 ± 0.008	37.9 ± 0.8	102.5 ± 3.8	-1.3 ± 0.4
- ,	T_2	50.8 ± 1.0	28.2 ± 0.6	7.372 ± 0.004	37.5 ± 0.6	106.1 ± 4.0	-2.8 ± 0.3
Both B	В	51.5 ± 0.3	29.2 ± 0.5	7.393 ± 0.013	38.2 ± 1.0	98.7 ± 3.5	-1.3 ± 0.5
	T_2	$20.2 \pm 0.4^{\circ}$	$11.3 \pm 0.3^{\circ}$	7.353 ± 0.007	35.5 ± 1.0	110.6 ± 6.6	-5.2 ± 0.6^{a}

B, baseline; T₂, 60 min after hemodilution and 30 min after infusion.

Table 3. Myocardial Performance After Preload and Afterload Stress Tests

	Control	Hemodilution	Verapamil	Both
Peak cardiac index (mL·min ⁻¹ ·kg ⁻¹)	396 ± 17	448 ± 6	322 ± 15 ^d	320 ± 19°
Peak stroke volume index (mL·beat ⁻¹ ·kg ⁻¹)	1.14 ± 0.02	1.30 ± 0.02^a	1.04 ± 0.03	1.22 ± 0.07^{b}
Left ventricular developed pressure (mm Hg)	210 ± 3	221 ± 4	160 ± 4^d	175 ± 10°

Values are expressed as mean ± sem.

though CI and oxygen availability were lower, and LVEDP and serum lactate levels were higher, compared with hemodiluted controls (29). Possible impairment in tissue oxygenation in that study may have been due to the lower levels of hemodilution used (hematocrit 15%), anesthetic agents (droperidol, fentanyl, piritramide, and nitrous oxide), and/or differences in volume status between groups (hemodiluted controls experienced a 20% increase in HR at hematocrits between 15% and 25%) (29). The anesthetic used in the present study (thiobutabarbital) was chosen because of the absence of any significant cardiovascular depression associated with it (17,18). Moreover, it is likely that normovolemic conditions existed in all animals in the present study after hemodilution because previous experiments have demonstrated the adequacy of hetastarch in maintaining circulatory blood volume (30–32). In addition, the lack of any significant change in HR after hemodilution in these animals supports the notion that normovolemia was maintained, as any HR increase may indicate insufficient infusion of the substitute solution or redistribution of the diluent extravascularly (1,3). Although the frequency response of the catheter-transducer system used to measure left ventricular pressure was low owing to an altered capacitance of the front end filter of one amplifier channel, this occurred in all treatment groups. Thus, intergroup comparisons are still valid, but left ventricular pressure data may have been underestimated because of filtering of higher frequencies such that comparison of our left ventricular pressure data with those in the literature should probably be avoided.

Although verapamil did not reduce the compensatory increase in CI and SVI after hemodilution, these measurements only represented resting cardiovascular parameters. It is generally accepted that myocardial performance in response to stress may be a more sensitive indicator of impairment in myocardial function (33). For example, the volume load test represented the pumping ability of the left ventricle, and eliminated the confounding effect of preload (34). The pressure load test represented the pressure-generating capability of the left ventricle and thus was independent of afterload changes induced by hemodilution (35). Compared with the hemodilutiononly group, verapamil reduced peak CI and left ventricular developed pressure in hemodiluted animals but was unable to alter the elevated peak SVI. It is possible that peak SVI remained elevated in group

Values are expressed as mean \pm sem. $^{*}P < 0.05$, baseline versus T_{2} .

 $^{^{}a}P < 0.05$, hemodilution versus control.

^bP < 0.05, both versus verapamil.

 $^{^{}c}P$ < 0.05, both versus hemodilution. ^{d}P < 0.05, verapamil versus control.

4 because of increased venous return and enhanced left ventricular emptying secondary to the lowered blood viscosity. This occurred despite verapamil's negative inotropic and chronotropic effect. These findings are in agreement with Crystal et al. (22), who found that the regional hyperdynamic circulatory response to hemodilution (including increased stroke volume and cardiac output) remained intact in dogs pretreated with propranolol despite this agent's negative inotropic and chronotropic effect. Similarly, Chapler et al. (36) and Tarnow et al. (37) were unable to demonstrate any deleterious effects of propranolol on the immediate hyperdynamic cardiovascular response to hemodilution, although other studies using lower levels of hemodilution (14%–16% hematocrit) and/or other anesthetic agents (halothane, pentobarbital) have demonstrated blunting or attenuation of the increased stroke volume and cardiac output during intravenous propranolol therapy (12,13,38). Although disopyramide-induced myocardial depression was shown to blunt the cardiac output and stroke volume response to hemodilution to hematocrits of 23% (14), depressed ventricular function after myocardial infarction in hemodiluted rats (hematocrit = 20%) only resulted in a more limited rise in CI (and did not affect stroke volume) compared with animals with normal ventricular function (11). However, in the presence of diminished coronary reserve (39), or increased oxygen requirements (e.g., aortic stenosis) (40), cardiac function may be more vulnerable to similar levels of acute normovolemic hemodilution.

The ability of verapamil to reduce SVR further in hemodiluted animals in the present study resulted in significant hypotension despite the compensatory increases in CI and SVI. Similar reductions in SVR by verapamil during hemodilution have been reported (29). This may be due to the biophysical membrane effects of calcium channel blockers on vascular smooth muscle (41-43), which include interference with α_1 - and α_2 -adrenergic receptor-mediated vasoconstriction and/or impairment of neurotransmitter release and ganglionic transmission (44 46). These effects may be in addition to the microcirculatory and macrocirculatory changes induced by normovolemic hemodilution that are related to changes in blood viscosity, shear stress, flow velocity, and vascular flow resistance at the level of the arterioles, capillaries, and venules (47).

The results of the present study indicate that reduction of myocardial contractility and cardiac performance produced by verapamil does not interfere with the compensatory increase in stroke volume after acute normovolemic hemodilution. However, extrapolation of these results to humans should be made cautiously. The effect of verapamil during normovolemic hemodilution represents a complex interaction among multiple factors such as the integrity of the cardiac conduction system, degree of hemodilution, sympathetic nerve activity, and circulating catecholamines. Moreover, the presence of cardiovascular disease (e.g., arrhythmia, myocardial ischemia) and other pharmacologic depressants (e.g., barbiturates, other anesthetic agents, β -adrenoceptor antagonists) may alter the response to verapamil during normovolemic hemodilution.

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Prevention of Postoperative Nausea and Vomiting Using Ondansetron, a New, Selective, 5-HT₃ Receptor Antagonist

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LEESER J, LIP H. Prevention of postoperative nausea and vomiting using ondansetron, a new, selective, 5-HT₃ receptor antagonist. Anesth Analg 1991;72:751–5.

The effect of ondansetron, a 5-HT_3 antagonist, in preventing postoperative nausea and vomiting was investigated in a randomized, double-blind, placebo-controlled study of 84 patients undergoing gynecologic operation and receiving the same general anesthetic. The patients received premedication with either 16 mg oral ondansetron, or a matching placebo. The same medication was given postoperatively 8 h after the first dose. During the first hour after recovery from anesthesia, the frequencies of nausea and vomiting were

52% and 40%, respectively, in patients given placebos. In the ondansetron group nausea and vomiting developed in 17% and 12%, respectively, values significantly different from those with placebos (P < 0.005). Similar differences were observed throughout the entire 24-h period after recovery, the incidence of nausea and vomiting being 67% and 60%, respectively, in the placebo group and 29% and 26% in the ondansetron treatment group. Ondansetron appears to be a promising antiemetic for the prevention of postoperative nausea and vomiting.

Key Words: VOMITING, ANTIEMETICS—ondansetron.

Nausea and vomiting are common after operative procedures requiring general anesthesia, with incidences that have remained unchanged over the last 30 yr (1).

Ondansetron is a serotonin antagonist that selectively inhibits 5-HT₃ receptors, with little or no activity on dopamine or other receptors (2). Both animal experiments (3) and studies in humans have shown ondansetron to be effective in preventing nausea and vomiting associated with cancer chemotherapy and radiation therapy (4–7). Because of its lack of activity at dopamine receptors, ondansetron has not been associated with extrapyramidal signs or symptoms often seen with antiemetics that act as dopamine antagonists, e.g., droperidol or metoclopramide. It may, therefore, have a potential benefit over such agents in the prevention of postoperative nausea and vomiting.

The effect of oral ondansetron in preventing postoperative nausea and vomiting in patients undergoing gynecologic operation under general anesthesia has, therefore, been investigated in a double-blind, randomized, placebo-controlled study.

Methods

This randomized, double-blind study was carried out at two centers (Onze Lieve Vrouwe Gasthuis, Amsterdam, and Sophia Ziekenhuis, Zwolle) in The Netherlands, and the institutional ethics committees at both centers gave their approval for the conduct of the study. Each patient gave her written consent to take part in the study.

A total of 84 patients, aged 18–65 yr, scheduled to have abdominal gynecologic operations under general anesthesia were included in the study. Patients who were pregnant or breast-feeding or who had evidence of clinically significant renal, hepatic, cardiovascular, metabolic, or endocrine dysfunction, or who had clinically significant abnormalities in laboratory screening tests, were excluded (patients of ASA physical status IV and V were thus excluded). In addition, patients who had received antiemetic medication in the 12 h before entering the study were excluded.

Patients were randomly allocated to receive either ondansetron (Glaxo Group Research Limited, U.K.)

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or placebo according to the patient number taken from a predetermined randomization list. Study medication, either 16 mg ondansetron (two 8-mg tablets) or placebo (two tablets) was administered with premedication approximately 1 h before operation. A second dose of 16 mg ondansetron or placebo was administered postoperatively 8 h after the first dose.

ANESTH ANALG

All patients were premedicated with 10 mg diazepam orally except for one patient who was given 5 mg diazepam.

Anesthesia was induced with 4–5 mg/kg thiopental and maintained using 67% nitrous oxide in oxygen supplemented with 0.8%-2.5% isoflurane. Analgesia, if required, was maintained with alfentanil, using doses up to 7.5 mg, and vecuronium bromide was used as a muscle relaxant. If required, reversal of muscle relaxation was achieved with 1 mg atropine and 2 mg neostigmine except for two patients in the placebo treatment group, one of whom was given 2 mg atropine and 2 mg neostigmine, and the other who was given 0.5 mg atropine and 1 mg neostigmine. Postoperative analgesia was provided by morphine.

All observations were made without knowledge of which treatment each patient received. Nausea and vomiting were assessed 1 h after recovery (as defined below), and again 24 h after recovery. Both nausea and vomiting were assessed separately, as present or absent. Nausea was assessed by a single individual at each center by asking whether the patient had experienced any nausea during the assessment period. The question was phrased in the same way for all patients. Records of patients who vomited were kept by the nursing staff. The severity of vomiting was not assessed. Retching was not assessed as a separate entity, and patients who reported retching were classified as nauseous. If patients experienced nausea or vomiting, they could request antiemetic treatment in the form of a 25-mg prochlorperazine maleate suppository.

The duration of anesthetic administration and the time to recovery from anesthesia (patients were considered to have recovered from anesthesia when they first responded to spoken command) were assessed. Vital signs, including respiratory rate, blood pressure, and pulse rate, were monitored during the study. The patients were questioned about any possible side effects of the study medication 24 h after the operation and again after 5-7 days, when routine blood and urine samples were obtained for laboratory screening before discharge of the patient from the hospital. Laboratory tests included measurement of serum levels of sodium, potassium, calcium, total protein, albumin, urea, creatinine, bilirubin, alkaline

Table 1. Patient Demography

	Placebo $(n = 42)$	Ondansetron $(n = 42)$
Age (yr)	43 ± 11	44 ± 10
Age range (yr)	23-61	21-60
Weight (kg)	69.6 ± 10.2	65.2 ± 10.9

Values for age and weight are expressed as mean ± sp.

phosphatase, alanine transaminase, aspartate transaminase, and γ-glutamyl transpeptidase. Blood samples were also obtained for measurement of hemoglobin content, red blood cell count, packed cell volume, mean cell volume, platelet count, total white cell count, and differential white cell count. Urine was analyzed for pH and the presence of protein and glucosé.

The sample size chosen was designed to detect a decrease in nausea and vomiting from 65% after placebo treatment to 25% after ondansetron treatment assuming type I and type II errors to be 0.05. Analysis of the incidence of nausea and vomiting was carried out using logistic regression from which the relative risk of each event occurring was obtained for ondansetron relative to placebo. For the purposes of analysis, any patient who had requested and received prochlorperazine was deemed a treatment failure and considered to have vomited. All patients were included in the analysis.

Differences in duration of anesthesia and the times to recovery were analyzed using the Wilcoxon rank-

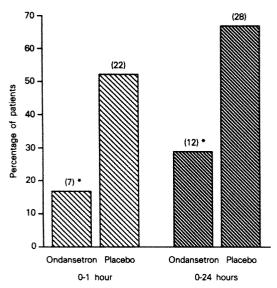
Blood pressures and pulse rates were averaged during the maintenance of anesthesia, emergence from anesthesia, and the postoperative period. Analysis of covariance was applied to the single measurement recorded at induction of anesthesia and to the average values obtained during the maintenance of anesthesia and during the emergence and postoperative periods. Blood pressure and pulse rate measured at the time of premedication, before administration of study drug, was used as a pretreatment covariate in each analysis. Respiratory rate was averaged during the emergence and postoperative periods.

Results

A total of 84 patients were entered into the study, 30 from one center and 54 from the other. The mean age and weight of the patients in the two treatment groups were not significantly different (Table 1).

<u>Table 2</u>. Types of Operation Performed in Each Treatment Group

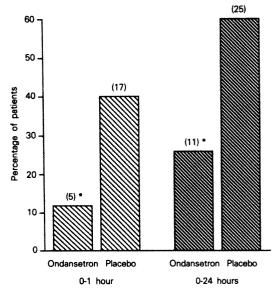
	Placebo $(n = 42)$	Ondansetron $(n = 42)$
Abdominal hysterectomy	22	26
Abdominal laparotomy	20	15
Vaginal hysterectomy	0	1



<u>Figure 1</u>. The percentages of patients treated with ondansetron and placebo who suffered nausea in the first hour and first 24 h after recovery. Actual numbers of patients in each group who suffered nausea are shown in parentheses; n=42 for both treatments. *Significantly different from placebo, P < 0.001.

The types of operations performed are presented in Table 2; the groups are well matched, with no important differences. One patient who had a vaginal hysterectomy was included in the analysis.

The incidence of nausea and vomiting during the first 24 h after operation is shown in Figures 1 and 2. As might be expected, the incidence of nausea was somewhat higher than the incidence of vomiting because several patients experienced nausea without vomiting, whereas no patients experienced vomiting without nausea. Ondansetron treatment resulted in a significantly lower incidence of both nausea and vomiting during the study period. During the first hour after recovery, the incidence of nausea was 52% in placebo-treated patients compared with 17% in the ondansetron-treated group, and the incidence of vomiting was 40% in the placebo group and 12% in the ondansetron-treated group, respectively. Similar results were observed when nausea and vomiting were assessed over the whole of the first 24 h postrecovery. The overall incidence of nausea in the placebo group during the 24-h period was 67% compared



<u>Figure 2</u>. The percentages of patients treated with ondansetron and placebo who vomited in the first hour and first 24 h after recovery. Actual numbers of patients in each group who vomited are shown in parentheses; n = 42 for both treatments. *Significantly different from placebo, P < 0.005.

<u>Table 3</u>. Relative Risk of Experiencing Nausea or Vomiting During the First 24 h Postoperation on Ondansetron Compared With Placebo

Relative risk of Time nausea ^a after (95% confidence recovery interval)		Relative risk of vomiting" (95% confidence interval)
0–1 h	0.18 (0.07, 0.50)	0.18 (0.06,0.58)
0-24 h	0.20 (0.08, 0.51)	0.24 (0.10, 0.61)

^aOndansetron compared with placebo.

with 29% in the ondansetron-treated group. Similarly, the incidence of vomiting during the whole 24-h period was 60% in the placebo-treated group and 26% in the ondansetron-treated group.

When the relative risk of suffering emetic sequelae was calculated, patients were found to be approximately one-fifth as likely to experience nausea or vomiting after ondansetron treatment compared with placebo (Table 3).

The number of patients who required antiemetic treatment was less in the ondansetron-treatment group than in the placebo group. A total of 12 doses of prochlorperazine were administered to eight patients in the ondansetron group, compared with 33 doses administered to 22 patients in the placebo group.

Patients in the first 24 h after recovery received postoperative analysesic medication with 10 mg intramuscular morphine with only a few exceptions (Table

Table 4. Analgesic Medication Administered During the First 24 h After Recovery

	Number of patients receiving					
	1 Dose	2 Doses	3 Doses	4 Doses	5 Doses	Total
Placebo	5	16 ^b	11	8	0	40
Ondansetron	5	15°	15	44	1	4 0

"All patients received 10 mg intramuscular morphine, unless otherwise

Includes one dose 10 mg piritramide and one dose 5 mg intramuscular

Încludes one dose 10 mg subcutaneous morphine.

Includes two doses 5 mg intramuscular morphine.

4). Both the ondansetron-treated group and the placebo group were given similar amounts of analgesic medication (Table 4). A total of 102 doses of narcotic analgesics were administered to patients in the placebo group and 101 doses to those in the ondansetron-treated group.

A total of 27 patients in the ondansetron-treated group had muscle relaxation reversed with atropine and neostigmine compared with 29 in the placebo group. The duration of anesthesia was comparable in both treatment groups, the mean period being 128 min (range, 35–290 min) in the placebo group and 125 min (range, 60–280 min) in the ondansetrontreated group. No significant differences in the time to recovery after anesthesia were observed, the mean time being 9 min (range, 4-30 min) after placebo treatment and 11 min (range, 0-55 min) after ondansetron treatment.

No clinically important changes in blood pressure, pulse rate, or respiratory rate occurred during the study. No side effects considered to be related to study medication were reported. One patient who received ondansetron had delayed recovery from anesthesia, and another developed ileal stasis and a wound infection. None of these events were considered to have occurred as a result of ondansetron treatment.

Occasional changes in laboratory values were seen postoperatively in both groups, 5–7 days after the operation, but in only four patients were these considered to be of any clinical significance. Three patients treated with ondansetron and one patient treated with placebo showed minor elevations in liver function tests.

Discussion

Postoperative nausea and vomiting are troublesome complications of anesthesia that have proved difficult to prevent. A variety of agents with differing phar-

macologic properties are used in everyday practice, among the most popular being antihistamine, e.g., cyclizine, anticholinergic, e.g., scopolamine, and antidopaminergic drugs, e.g., droperidol. All the compounds available at present, however, have significant side effects that have frequently limited their use to the treatment of emesis rather than prophylactic use (8,9). The present paper describes the antiemetic properties of a novel class of compound, a 5-HT₃ receptor antagonist, which appears to be devoid of many of the side effects known to be associated with existing antiemetics.

Ondansetron has already proved to be an effective treatment for the prevention of nausea and vomiting induced by cancer chemotherapy and radiotherapy (4-7). The present study provides evidence that it is also effective in reducing the nausea and vomiting that occur after anesthesia. The fact that the relative risks of experiencing either nausea or vomiting after ondansetron treatment compared with placebo were similar demonstrates that the compound was equally effective, in proportional terms, against both symp-

Many factors may influence the incidence of postoperative nausea and vomiting, and in the present study care was taken to ensure that the treatment groups were comparable in terms of type of patient, demography, surgical procedure, and type of anesthesia used. Similarly, the consumption of opiate analgesics was closely monitored to ensure that differences between the groups could not account for any difference in the incidence of emesis. It is concluded that oral treatment with ondansetron was effective in reducing the incidence of both postoperative nausea and vomiting in comparison with placebo treatment over the 24-h observation period.

The site of action of ondansetron in the prevention of postoperative emesis is uncertain. It has been shown in animals that the area postrema and parts of the nucleus tractus solitarius, adjacent sites in the brain known to be associated with nausea and vomiting, contain large numbers of 5-HT₃ receptors (10,11), and it is possible that ondansetron may act at these sites to reduce emesis. A peripheral action in the gastrointestinal tract at afferent vagal fibers known to possess 5-HT₃ receptors cannot be ruled out. Further studies will be required to elucidate the exact site of action or, indeed, whether there are both central and peripheral actions involved in the control of emesis by 5-HT₃ antagonists.

Ondansetron would appear to be a promising agent for the prevention of postoperative nausea and vomiting, as it is both effective and devoid of many of the side effects associated with current therapies,

including dopamine antagonists. Further studies will need to be performed to establish its optimal dosage.

Glaxo Group Research Limited generously supplied ondansetron and matching placebo tablets, in addition to financial support for laboratory investigations and statistical analysis.

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Comparison of Sufentanil and Fentanyl to Supplement N_2 O-Halothane Anesthesia for Total Hip Arthroplasty in Elderly Patients

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GAUZIT R, MARTY J, COUDERC E, BOUYET I, FLAISLER B, DESMONTS JM. Comparison of sufentanil and fentanyl to supplement N₂O-halothane anesthesia for total hip arthroplasty in elderly patients. Anesth Analg 1991;72:756–60.

Sufentanil was compared with fentanyl as a supplement to nitrous oxide-halothane anesthesia in a double-blind study of 30 elderly patients undergoing total hip arthroplasty. Comparisons were made with respect to (a) hemodynamic (heart rate and blood pressure) and adrenergic (plasma norepinephrine and epinephrine levels) responses during surgery and recovery; (b) time to extubation after the end of surgery; and (c) postoperative analgesia. No difference was observed between the two groups with respect to demographic data, blood gas tensions, or hemodynamic and

adrenergic responses to surgery and recovery. Total doses of opioids used were 0.7 ± 0.3 µg/kg of sufentanil and 6 ± 2.6 µg/kg of fentanyl. Times between end of surgery and extubation were not different (60 ± 54 min in the fentanyl group and 58 ± 52 min in the sufentanil group). The number of patients needing postoperative analgesia did not differ between the two groups, but use of analgesia was significantly delayed in the sufentanil group (168 ± 25 vs 127 ± 29 , P < 0.05). This study suggests that in elderly patients sufentanil confers a greater residual analgesia than fentanyl in the immediate postoperative period.

Key Words: ANESTHETICS, INTRAVENOUS—sufentanil, fentanyl. ANESTHETICS, VOLATILE—halothane. ANESTHESIA, GERIATRIC.

Sufentanil, the N4 thienyl derivative of fentanyl, has been proposed for clinical practice as an alternative to fentanyl. It has a shorter half-life (a $T_{1/2\beta}$ of 150 min) than fentanyl (a $T_{1/28}$ of 220 min) and a greater potency (1,2). Several comparative studies have been conducted in different situations to determine the clinically relevant differences between fentanyl and sufentanil. Most reports show that sufentanil and fentanyl are associated with similar hemodynamic and adrenergic responses during and after operation in patients undergoing cardiac or noncardiac operations (3–11). By contrast, conflicting results have been reported concerning the duration of postanesthetic respiratory depression (3-6). Similar discrepancies have been observed regarding the effects of sufentanil and fentanyl on residual analgesia (3-6). However, a dissociation between the pharmacologic effects of sufentanil on respiration and its analgesic properties has been recently demonstrated (12). Because increased sensitivity to opioids has been documented in elderly patients (13), it might be expected that differences between sufentanil and fentanyl may be greater in elderly patients. Therefore, the present study was designed to compare, in a double-blind controlled trial, sufentanil and fentanyl to supplement nitrous oxide (N_2O)-halothane anesthesia in elderly patients.

Methods

Thirty patients (age range, 62–87 yr), ASA physical status I and II, undergoing total hip arthroplasty were randomly allocated to receive either sufentanil (n = 15) or fentanyl (n = 15). None was receiving β -adrenergic blocking agents or diuretics. Institutional approval was obtained, and all patients gave informed consent. Premedication consisted of 2.5 mg oral

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lorazepam and 1 mg atropine 1 h before operation. On the patient's arrival in the operating room, a peripheral venous catheter was inserted, as well as a radial artery catheter, for measurement of arterial blood pressure and collection of blood samples. Heart rate and lead II electrocardiogram were continuously displayed. A temperature probe was inserted in the esophagus.

Anesthesia was induced by 4 mg/kg thiopental, followed by 1 mg/kg succinylcholine to facilitate tracheal intubation. Controlled ventilation was then started with a tidal volume of 8 mL/kg at a respiratory rate of 12-16 breaths/min. Anesthesia was maintained by inhalation of a mixture of N_2O -oxygen (O_2) (60%:40%) plus halothane (inspired concentration, 0.5%) until the end of the operation. Fluid management and transfusion to obtain an hematocrit of ~30% at the end of the operation were similar in all cases. Fentanyl (50 μ g/mL) or sufentanil (7.5 μ g/mL) in an unmarked syringe was administered by the attending anesthesiologist during the operation whenever systolic and diastolic arterial pressures (SAP, DAP) or heart rate (HR) increased 15% or more above values recorded during steady-state anesthesia before the beginning of the surgical procedure. The last administration of narcotic was made no later than the placement of the femoral prosthesis (30–45 min before the end of the operation). The trachea was extubated in the recovery room using the usual clinical criteria, after which nasal oxygen therapy (2 L/min) was initiated. Systolic arterial pressure, DAP, HR, and esophageal temperature were recorded just before induction, immediately after endotracheal intubation, after skin incision, at the time of hip arthroplasty, before skin closure, just after extubation, and then twice an hour until the fourth hour after tracheal extubation. Arterial blood samples for subsequent determination of plasma norepinephrine or epinephrine levels by high-performance liquid chromatography (14) were collected at the same times. Blood gas tensions were measured before induction, during anesthesia, and 1 and 2 h after extubation. During recovery, pain was assessed on a four-degree scale (0 = no pain, 3 = severe pain) at the same time that blood gas tensions were measured. Morphine chlorhydrate (7-10 mg) was administered subcutaneously when the pain score was 1 or more.

Clinical characteristics between the two groups were compared using t-test or χ^2 -analysis. Mean values \pm sp for HR, SAP, DAP, esophageal temperature, plasma norepinephrine and epinephrine levels, and blood gases were calculated at each time of the study. Comparisons in each group and between the two groups were made by analysis of variance

Table 1. Clinical Data

	Sufentanil $(n = 15)$	Fentanyl $(n = 15)$
Age (yr)	69 ± 7	74 ± 7
Sex ratio (F/M)	6/9	7/8
ASA physical status (I/II)	13/2	12/3
Duration of anesthesia (min)	164 ± 38	183 ± 32
Total doses of opioids used (μg/kg)	0.71 ± 0.29	6.0 ± 2.6

Values for age, duration of anesthesia, and total doses of opioids used are expressed as mean \pm sp.

followed by Bonferroni's adjusted *t*-test. Nonparametric analysis (Mann–Whitney) was used to compare times to extubation, times until administration of morphine, and pain score. A *P* value less than 0.05 was considered to be significant.

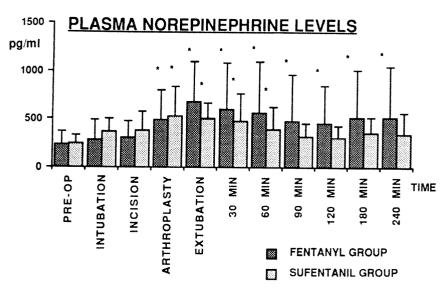
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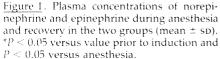
Clinical characteristics of the two groups are summarized in Table 1. The two groups did not differ significantly with respect to age, sex ratio, ASA physical status, or duration of anesthesia. In addition, no significant difference was observed regarding baseline data (Figure 1, Table 2). The mean total doses of sufentanil and fentanyl administered during operation (Table 1) suggest that the equipotency ratio is about 8.

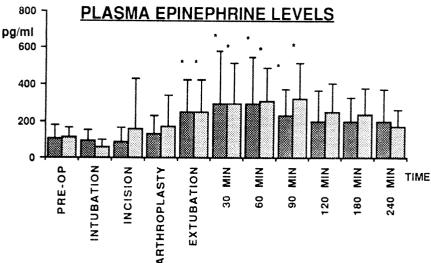
Arterial pressure and heart rate were not significantly different at any time during operation and recovery (Table 2). In both groups, SAP and DAP decreased significantly below baseline levels during steady-state anesthesia (maximal changes, -25% and -10%, respectively). Systolic arterial pressure and DAP were significantly above levels just before the end of the operation at the time of extubation and during early recovery. These values, however, were not significantly different from those obtained before anesthesia. By contrast, SAP and DAP recorded during the late recovery period were significantly lower than baseline levels. In the two groups, a significant but transient increase in HR was observed at the times of intubation and extubation.

Plasma concentrations of norepinephrine and epinephrine (obtained in 11 patients in each group) were similar in the two groups throughout the study period (Figure 1). During operation, plasma levels of norepinephrine and epinephrine remained stable. However, at the end of anesthesia and during the early recovery, values of norepinephrine and epinephrine increased significantly in both groups above

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baseline levels. During late recovery, plasma norepinephrine concentrations remained significantly elevated only in the fentanyl group.

Esophageal temperature was similar in the two groups during the entire study (Table 3).

There were no differences in times to extubation in the two groups (fentanyl group, 60 ± 54 min; sufentanil group, 58 ± 52 min). Blood gas tensions were also similar in both groups. Paco₂ increased significantly but moderately above baseline levels 60 min after extubation (Table 4). Postoperative pain scores were not significantly different. The administration of morphine was necessary in 9 patients in the fentanyl group and in 10 patients in the sufentanil group. However, the need for additional analgesic postoperatively was significantly delayed in the sufentanil group (Table 5).

Discussion

The results of this double-blind controlled trial were that in elderly patients only few differences were observed between sufentanil and fentanyl when used to supplement N₂O-halothane anesthesia for noncardiac surgery. Briefly, no difference was observed between the two groups regarding cardiorespiratory and adrenergic responses during operation and recovery. In contrast, a longer residual analgesic effect was found in patients given sufentanil.

Previous reports comparing fentanyl and sufentanil alone or as a supplement to N_2O anesthesia in noncardiac or cardiac operations have suggested that hemodynamic and adrenergic responses to operation are similar (2–8). However, the conditions of the present study were different because it was per-

Table 2. Hemodynamic Data During Anesthesia and Recovery in the Fentanyl and Sufentanil Groups

	Systolic arterial pressure (mm Hg)		Diastolic arterial pressure (mm Hg)		Heart rate (beats/min)	
	F	S	F	S	F	S
Preoperative	165 ± 23	154 ± 17	79 ± 11	76 ± 14	79 ± 9	74 ± 11
Intubation	144 ± 33°	$138 \pm 27^{\circ}$	75 ± 16	74 ± 13	84 ± 18	83 ± 13^{a}
Incision	123 ± 25°	121 ± 19^a	70 ± 8"	$68 \pm 10^{\circ}$	$70 \pm 11^{\circ}$	66 ± 12^a
Arthroplasty	132 ± 19^{4}	130 ± 19"	77 ± 7	71 ± 11	68 ± 10°	67 ± 7
End of operation	122 ± 26^{a}	116 ± 27"	72 ± 14"	69 ± 12^{a}	71 ± 10"	65 ± 8^{a}
Extubation	164 ± 35^b	154 ± 24^b	82 ± 13^{b}	77 ± 14^b	$90 \pm 13^{a,b}$	$93 \pm 20^{a,b}$
Recovery						
15 min	158 ± 36^{b}	141 ± 22^{b}	76 ± 15	70 ± 12	85 ± 16^{b}	$84 \pm 19^{a,b}$
30 min	151 ± 31^{b}	$139 \pm 19^{a,b}$	77 ± 12	69 ± 10	80 ± 14^b	84 ± 17"
60 min	$142 \pm 29^{a,b}$	135 ± 21^a	70 ± 13°	$62 \pm 10^{\circ}$	75 ± 16	75 ± 17*,b
90 min	$129 \pm 20^{\circ}$	$130 \pm 20^{\circ}$	64 ± 11°	63 ± 9°	76 ± 13	75 ± 15^{b}
120 min	$131 \pm 21^{\circ}$	124 ± 22^a	68 ± 12^{a}	62 ± 11^{a}	75 ± 15	75 ± 15^{b}
150 min	132 ± 22"	125 ± 20°	65 ± 10 "	$62 \pm 10^{\circ}$	77 ± 14	77 ± 16^{b}
180 min	$130 \pm 23''$	123 ± 23*	66 ± 9^{a}	61 ± 13*	79 ± 15	82 ± 16^{b}
210 min	$130 \pm 16^{\circ}$	129 ± 21^a	66 ± 8°	62 ± 9"	80 ± 14	79 ± 14^b
240 min	127 ± 17*	127 ± 22^a	66 ± 9°	62 ± 7°	79 ± 15	77 ± 12^b

F, fentanyl; S, sufentanil.

Table 3. Esophageal Temperature in the Two Groups

	Fentanyl	Sufentanil
Preoperative	36.3 ± 0.4	36.3 ± 0.2
Intubation	36.0 ± 0.4	35.9 ± 0.3
Incision	35.6 ± 0.7	35.6 ± 0.4
Arthroplasty	35.4 ± 0.6	35.4 ± 0.4
End of operation	35.0 ± 0.7	35.0 ± 0.8
Extubation	34.4 ± 0.8	34.5 ± 1.5
Recovery		
15 min	34.5 ± 0.8	34.7 ± 1.5
30 min	34.7 ± 0.8	35.0 ± 1.4
60 min	35.1 ± 1.1	35.6 ± 1.1
90 min	35.5 ± 1.1	36.0 ± 1.1
120 min	35.8 ± 1	36.3 ± 1
150 min	36.2 ± 1	36.6 ± 1
180 min	36.4 ± 0.9	36.7 ± 1
210 min	36.7 ± 0.8	37.1 ± 0.8
240 min	36.9 ± 0.7	37.2 ± 0.9

Values are expressed as mean ± sp.

formed in elderly patients during N₂O-halothane anesthesia and with moderate doses of sufentanil and fentanyl. Elderly patients have been reported to have alterations in hemodynamic responses to operation and anesthesia (13). Our data demonstrate that in these patients, sufentanil and fentanyl are comparable in their ability to attenuate hemodynamic and adrenergic responses to operation. Some reports have documented differences between sufentanil and fentanyl in their ability to maintain hemodynamic stability. These differences might have been related to different ratios between the doses of sufentanil and

fentanyl. Most investigators reported a dose ratio of between 5:1 and 10:1, whatever the absolute doses used (3–8). We found an 8:1 dose ratio, but it was not predetermined because administration was blinded. Therefore, it is not surprising that similar responses were observed during operation because opioids were administered when and as necessary to maintain hemodynamic stability. More interesting is the fact that postoperative hemodynamic and adrenergic responses during recovery were similar until the fourth hour after tracheal extubation. Most studies evaluated only hemodynamic responses during anesthesia or during the immediate recovery period, whereas cardiovascular complications are more frequent later.

By contrast, differences concerning postoperative respiratory depression and residual analgesia could have been expected because elimination of sufentanil is more rapid than elimination of fentanyl. Indeed, alterations in the pharmacokinetics of opioids have been described in elderly patients (13), as well as an increased sensitivity to opioids. However, no clinically relevant difference regarding respiratory depression has been observed in the present study. Times to extubation were similar, and so were blood gas tensions measured 1 h after tracheal extubation. More sensitive methods might have detected slighter changes, but our data are similar to other previously reported data based on rebreathing methods or occlusion pressure (3,15).

Values are expressed as mean ± sp.

P < 0.05 versus preoperative value.

 $^{^{}b}P < 0.05$ versus anesthesia value (end of operation).

Table 4. Blood Gas Tensions

	Control	Anesthesia	Recovery + 60 min	Recovery + 120 min
Fentanyl				
pН	7.39 ± 0.03	7.39 ± 0.03	7.33 ± 0.02	7.35 ± 0.05
Paco ₂ (kPa) ^a	5 ± 1	5 ± 0.4	5.5 ± 0.7 ⁶	5.4 ± 0.7^{b}
Pao ₂ (kPa)"	14 ± 9	21 ± 6	13 ± 2	12 ± 3
HCO ₃ (mEq/L)	23 ± 3	22 ± 2	21 ± 2	22 ± 3
Sufentanil				
pН	7.4 ± 0.03	7.4 ± 0.06	7.34 ± 0.05	7.35 ± 0.04
Paco₂ (kPa)⁴	5 ± 0.4	4.9 ± 0.9	5.5 ± 0.6^{b}	5.4 ± 0.4^{b}
Pao ₂ (kPa)	12 ± 1	22 ± 4	15 ± 3	14 ± 4
HCO_3^- (mEq/L)	24 ± 1	22 ± 2	22 ± 2	22 ± 2 ,

Values are expressed as mean ± sp.

Table 5. Postoperative Analgesia

	Fentanyl	Sufentanil
Patients requiring morphine (n)	10	9
Time until administration of morphine (min)	127 ± 29	168 ± 25°

Values for time until administration of morphine are expressed as mean

The most interesting finding in the present study concerns residual analgesia. Pain scores were not different and the number of patients requiring additional analgesia were identical, but the need for morphine postoperatively was significantly delayed in the sufentanil group. This cannot be explained easily on the basis of the pharmacokinetic properties of the two drugs. Further studies are required to explain this phenomenon, which has been reported in younger patients by Clark et al. (3).

In conclusion, in elderly patients, sufentanil and fentanyl used to supplement N_2 O-halothane anesthesia did not lead to any clinically relevant difference regarding cardiorespiratory responses to operation or recovery. A longer analgesic effect during recovery was, however, seen with sufentanil.

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 $^{^{\}circ}$ kPa × 7.5 = mm Hg.

 $^{^{}b}P < 0.05$ versus the control value.

^{*}P < 0.01 versus fentanyl group.

Ventilatory Response to Carbon Dioxide After Epidural Clonidine Injection

Catherine Penon, MD, Claude Ecoffey, MD, and Sheila E. Cohen, MB, ChB

PENON C, ECOFFEY C, COHEN SE. Ventilatory response to carbon dioxide after epidural clonidine injection. Anesth Analg 1991;72:761–4.

The authors studied the effects of epidural clonidine (300 µg) on circulation and ventilatory control in seven healthy unpremedicated subjects. After clonidine injection, arterial blood pressure decreased significantly in all subjects (range, 13%–25% for systolic blood pressure and 13%–32% for diastolic blood pressure). Heart rate decreased significantly by 10%–16% between 75 and 105 min after

injection. The slope of the ventilatory response to CO_2 decreased significantly from 2.06 \pm 0.70 (baseline) to 1.37 \pm 0.68, 1.25 \pm 0.65, and 1.33 \pm 0.67 L·min⁻¹·mm Hg⁻¹ (mean \pm sd, P < 0.05) at 15, 60, and 120 min. The authors conclude that epidural clonidine induces mild ventilatory and circulatory depression.

Key Words: SYMPATHETIC NERVOUS SYSTEM, PHARMACOLOGY—clonidine. ANESTHETIC TECHNIQUES, EPIDURAL—clonidine.

Clonidine, an α_2 -adrenergic agonist, has, when given epidurally, potent analgesic properties that could replace or augment the analgesia produced by epidural opioids (1,2). Clonidine modifies transmission of pain by activating presynaptic and postsynaptic α_2 -adrenoreceptors in the spinal cord. Preclinical toxicity testing of epidural clonidine is reasonably complete (3), and animal data suggest that it is safe (4–6).

Several recent reports have demonstrated the efficacy of epidural clonidine in producing postoperative analgesia (7–9). Dose-response data suggest that doses in the range of 300–700 μ g are necessary in this circumstance. Although, intrathecally administered opioids can be associated with side effects such as sedation and life-threatening respiratory depression, little information exists concerning the respiratory effects of epidural clonidine. The goal of this study was to determine the ventilatory effects of epidural clonidine.

Study Population

The protocol received institutional approval, and informed consent was obtained from all patients. Seven ASA physical status I male patients scheduled for minor orthopedic procedures (arthroscopy) were studied during an open trial. Their mean (\pm sD) age, weight, and height were 32 \pm 7 yr, 63 \pm 5 kg, 170 \pm 5 cm, respectively. Subjects had no clinical evidence of respiratory, cardiovascular, hepatic, or central nervous system disorders; they received no medication before the study and had fasted overnight.

Procedure for Epidural Injection

Ringer's lactate solution (3 mL·kg⁻¹·h⁻¹) was infused through an 18-gauge venous catheter. The electrocardiogram was continuously displayed on an electrocardioscope, and arterial blood pressure was measured by an automated sphygmomanometer cuff. With patients in the sitting position, an epidural catheter was inserted through a 17-gauge Tuohy needle at the L3-4 interspace. The patient was placed in the supine position with a head-up tilt of 45°.

One hour later, after a control set of measurements, clonidine (300 μ g) in 10 mL of normal saline solution was injected through the epidural catheter after a negative aspiration test. At the conclusion of

Methods

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the study, local anesthetics were injected through the epidural catheter to provide surgical anesthesia. All patients obtained effective anesthesia for operation.

Clinical Effects

Heart rate and systolic and diastolic arterial blood pressures were recorded before injection (baseline), at 15 and 60 min after injection, and every 15 min thereafter. All patients had oxygen saturation (Spo₂) monitored with a pulse oximeter (Nellcor N 100).

Ventilatory Measurements

A CO₂ stimulation test was performed in all subjects on the day before the study to familiarize them with the measurement technique. Results of this test are not included in the data. Ventilatory measurements were performed before (baseline) and 15, 60, and 120 min after epidural clonidine injection. Tidal volume (VT), respiratory rate (RR), and minute ventilation (VE) were recorded. A mouthpiece and nose-clip were used, and subjects breathed through a pneumotachograph (Fleisch No. 2) and a Rudolph nonrebreathing valve. Instrument dead space was 70 mL. Ventilatory response to CO₂ was assessed by rebreathing for 4–5 min from a 7-L spirometer filled with a mixture of 7% CO₂ in O₂. Volume was measured by electronically integrating the flow signal obtained from a Godart 17212 differential pressure transducer (Bilthoven, Holland) connected to a pneumotachograph previously calibrated with a 1 L syringe of air. End-tidal CO2 tension (Perco2) was measured with a Godart capnograph (Bilthoven, Holland) calibrated with a 7% mixture of CO₂ in O₂, verified to be accurate within 1% using Scholander microanalysis. All signals were recorded on a Gould ES 1000 recorder using a paper speed of 10 mm/s. Total cycle duration was measured from the flow signal. After converting ventilatory variables to BTPS, linear regression equations were computed from VE and from Petco₂ for each CO₂ challenge curve. The correlation coefficients ranged from 0.87 to 0.94.

Statistical Analysis

Differences between variables (arterial blood pressure, heart rate, and respiratory parameters) at each time interval and baseline values were tested using repeated-measures analysis of variance followed by Student's *t*-test with the Bonferroni correction.

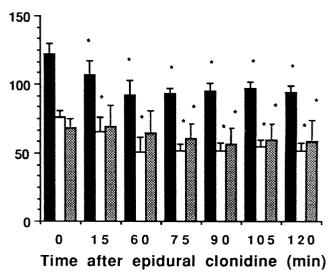


Figure 1. Systolic blood pressure (\blacksquare , mm Hg), diastolic blood pressure (\square , mm Hg), and heart rate (\square , beats/min) (mean \pm sp) after epidural injection of 300 μ g of clonidine. *P < 0.05 vs baseline.

P values < 0.05 were considered statistically significant.

Results

One hour after injection, all patients were asleep and clinical signs of upper airway obstruction were observed in five patients.

Statistically significant decreases in arterial blood pressure were seen in all subjects at each time during our study. Systolic blood pressure decreased by 13%–25% of baseline values and diastolic blood pressure by 13%–32% (Figure 1). Heart rate also decreased by a statistically significant degree (by 10%–16%) between 75 and 105 min after injection (Figure 1).

Ventilatory variables are summarized in Table 1. Epidural clonidine did not change resting RR, VE, and Petco₂. The Ve/Petco₂ slope decreased significantly compared with the baseline values at 15, 60, and 120 min after epidural clonidine injection. Spo₂ was always $\geq 95\%$. Apneic periods lasting more than 10 s occurred between 1 and 2 h after epidural clonidine injection in two patients, both while breathing room air and during CO₂ rebreathing.

Discussion

This study shows that clonidine administered epidurally depresses circulation and ventilatory drive, as

Table 1. Respiratory Variables Before and After Epidural Clonidine Injection

Variables	Baseline	15 Min	60 Min	120 Min
Resting Perco ₂ (mm Hg)	35 ± 3	33 ± 4	35 ± 4	32 ± 5
Resting RR (breaths/min)	15 ± 5	17 ± 5	16 ± 5	16 ± 4
Resting VE (L/min)	9.3 ± 2.4	9.8 ± 4.4	8.8 ± 3.1	9.4 ± 4
Slope Ve/Petco2	2.06 ± 0.7	$1.37 \pm 0.68^{\circ}$	$1.25 \pm 0.65^{\circ}$	$1.33 \pm 0.67^{\circ}$
$(L \cdot min^{-1} \cdot mm Hg^{-1})$				

 $Perco_2$, end-tidal CO_2 tension; RR, respiratory rate; Ve, minute ventilation. All values are mean \pm sd.

assessed by the rebreathing method. A control group was not studied because we believed there was no justification for performing a similar study with an epidural placebo injection.

The decreases in blood pressure and heart rate observed were similar to those previously reported (7,8,10). Hypotension after epidural clonidine injection is due to an inhibition of preganglionic sympathetic nerve activity in the spinal cord (11) as well as to inhibition of sympathetic and stimulation of parasympathetic nervous system activities in the brainstem (12). The latter effects may be the result of rostral spread of clonidine after epidural injection. The decrease in heart rate is due both to a direct effect on the heart and to central mechanisms. Delayed sedation 1 h after injection is probably also due to cephalad spread, as has been reported in other studies (7,10,13).

In a previous investigation in human subjects, intravenous clonidine injection did not alter Pao₂ or oxyhemoglobin levels (14). However, in an earlier study we found that oral administration of clonidine induced sedation with decreases in minute ventilation and with more periods of obstructive apnea and paradoxic breathing than what occurred with sleep alone (15). Rouge et al. also described a decrease in the ventilatory response to CO₂ after oral clonidine premedication (16), although Sperry et al. found no change in ventilatory drive in a similar study (17). The results in the present study, i.e., a decrease in the slope Ve/Perco₂ after injection of 300 μ g of epidural clonidine, is in accordance with those of Rouge et al. (16). Because measurement of ventilatory response to CO₂ is a sensitive test of respiratory depression, it may be abnormal when other less sensitive indices remain unaffected. For example, Eisenach et al. reported no change in arterial Pco₂ 1 h after epidural clonidine injection (10).

A possible explanation for the mild respiratory depression we observed is that it is due to the sleeping state. Moote and colleagues demonstrated that respiratory depression produced by morphine is dose-dependent and is potentiated by non-REM sleep (18). Clonidine suppresses REM sleep in a dose-dependent manner and increases the duration of non-REM sleep (19). Therefore, respiratory depression after epidural clonidine injection may be due either to an increase in non-REM sleep or to a direct effect of clonidine on the respiratory centers. The fact that sedation occurred after the decrease in the slope Ve/Petco₂ suggests that the latter mechanism is partly responsible for the effect.

In conclusion, although respiratory depression is probably mild, the decrease in the slope VE/Petco₂ and the occurrence of apneic episodes suggest that respiratory monitoring may be advisable after epidural clonidine injection. Further studies are needed to elucidate the exact mechanism for this effect and to determine the incidence of life-threatening respiratory depression.

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Feasibility of Epidural Morphine for Postoperative Analgesia in a Small Community Hospital

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CROSS DA, HUNT JB. Feasibility of epidural morphine for postoperative analgesia in a small community hospital. Anesth Analg 1991;72:765–8.

The first 6-mo experience of a two-physician APS using primarily epidural morphine in a community hospital is presented. After-hours anesthesia coverage was from home. The only monitoring was by nursing service observation. Complications occurred at incidences comparable to larger

studies. Using the precautions outlined in the text, complications were appropriately diagnosed and treated despite the lack of 24-h in-house anesthesia coverage.

Key Words: ANESTHETIC TECHNIQUES, EPIDURAL—morphine. PAIN, POSTOPERATIVE—epidural morphine. ANALGESICS, MORPHINE—epidural.

Many studies have shown the benefits and hazards of epidural opioids. Ready et al. (1) established guidelines for acute pain services (APS) that included epidural opioids. However, most APS reports have come from institutions with 24-h in-house availability of anesthesiologists. In many small community practices, such coverage is impractical. We questioned whether our lack of full-time in-house availability of anesthesiologists should prohibit the establishment of an APS using primarily epidural opioids. If we established such an APS:

- 1. Would our incidence of complications be unacceptably high compared with the more traditional use of parenteral opioids?
- 2. Can additional systemically administered opioids be used with epidural morphine?
- 3. Can we detect respiratory depression using clinical criteria without special monitors?
- 4. Is there additional overall risk using epidural morphine analgesia as part of postoperative pain management?

Methods

Our two-man department of anesthesiology practices in a typical 200-bed community hospital as part of an independent multispecialty clinic. Night calls are taken from home with a usual response time of 20 min or less, and in-house physician coverage is provided by the emergency room physicians.

Pain Management Service

Our APS was patterned similarly to that described by Ready et al. (1). Having no suitable infusion pumps, we used morphine as our primary epidural opioid. All patients having abdominal, thoracic, or orthopedic operations were considered for inclusion in the APS. The hospital has no institutional procedural review committee. However, we worked closely with the participating surgeons, hospital administration, and nursing service in the implementation of protocols. Our results have been continually reviewed by the hospital's Quality Assurance Committee. Informed consent was obtained from all patients included in the APS. Participating surgeons cooperated with our pain management.

Lumbar epidural catheters were inserted either just before or immediately after operation. Intraoperative heparin administration was not considered a contraindication for catheter placement. No efforts were made to alter the intraoperative anesthetic techniques in any way. Catheters were usually removed after 2–3 days. In only two patients were catheters

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maintained for 4 days. The single dose of morphine most frequently used was 5.0 mg but was adjusted for age, degree of pain relief obtained, and overall condition of the patient. Occasionally, additional epidural opioids, including hydromorphone, fentanyl, and sufentanil, were used at the discretion of the anesthesiologist for more rapid onset of pain relief. In addition, supplemental doses of intravenous morphine (1-2 mg) were occasionally given as needed for patient comfort. No local anesthetics were administered with the epidural opioids. Anesthesiologists always reinjected epidural opioids. Patients given epidural opioids were monitored in the same manner as those receiving parenteral opioids. Hospital rounds on APS patients were made in the mornings and additionally as needed.

Standing orders included documentation of vital signs at appropriate intervals and treatment protocols for minor complications. Complications not covered by standing orders were relayed to the in-house anesthesiologist during the day and the on-call anesthesiologist after hours. Respiratory depression was defined as a respiratory rate of less than 10 breaths/ min with a decreasing trend and an increasing somnolence as judged by the nursing staff. Monitoring for delayed respiratory depression consisted entirely of nurses' observation of the patients. Intravenous naloxone in 0.4-mg boluses as needed for reversal of delayed respiratory depression was administered when necessary by either the anesthesiologist or by a floor nurse after discussion with the anesthesiologist. In either case, our policy was to return immediately to the hospital to examine patients suspected of having delayed respiratory depression.

Chart Review

We evaluated our care of all patients (24 women and 28 men) in the APS within 6 mo using a retrospective chart review. Our major emphasis was to review the incidence of major complications.

Results

Operative procedures are listed in Table 1. The ages by decade are presented in Table 2. One hundred ninety doses of epidural morphine were administered. All patients were ASA physical status I–III with the exception of one ASA IV patient. The only death was the ASA IV patient who died of causes unrelated to APS.

A few patients occasionally required supplemental doses of intravenous opioids in the recovery room

Table 1. Operative Procedures

Procedure	Total No.	No. of APS	Percent of APS
Radical retropubic prostatectomy	10	6	60
Aortobifemoral graft	11	6	55
Cholecystectomy	64	12	19
Gastrectomy	7	2	29
Lower abdominal operation	40	16	4 0
Thoracotomy	12	6	50
Hip/lower extremity	14	4	29

Table 2. Ages by Decade

Age (yt)	No. of patients
20–29	2
3039	4
40-49	6
50-59	8
6069	17
7079	10
8089	5

Table 3. Minor Complications

Complication	No. of patients	%
Pruritus	10	19
Nausea	9	17
Urinary retention requiring catheterization	6	12
Superficial infection (after removal of catheter)	1	2
Accidental dislodgement of catheter by patient	1	2
Persistent inadequate pain relief	1	2

and within the first 10 h for temporary inadequate pain relief with epidural morphine.

Minor Complications

The incidences of minor complications are listed in Table 3. There were no long-term sequelae.

Major Complications

One 62-yr-old patient accidentally received 4.0 mg of epidural morphine intrathecally. The intrathecal placement of the catheter was discovered on aspiration through the syringe after injection. The patient suffered no respiratory depression. Subsequent morphine doses were tailored for intrathecal administration with continued good pain relief.

Early respiratory depression developed in the recovery room in two patients who received intraoperative epidural and parenteral opioids. As both patients had received epidural morphine shortly before the end of operation, it is unlikely that it was the sole cause of the early respiratory depression. Neither patient received parenteral opioids in the recovery room. Reversal of their respiratory depression with low-dose naloxone did not seem to alter the degree of pain relief from the epidural morphine.

The only patient in whom delayed respiratory depression developed had received no postoperative parenteral opioids nor other sedatives, had no history or symptoms of respiratory disease, and had had no clinical respiratory depression in the recovery room. Eight hours after 5.0 mg of epidural morphine was given intraoperatively, the patient became somnolent but arousable, with a respiratory rate of 10 breaths/ min, which decreased over the next hour. The situation was discussed with the on-call anesthesiologist, who confirmed the diagnosis by arterial blood gas tensions (Paco₂, 67 mm Hg) and by examination of the patient. The respiratory depression was reversed with intravenous naloxone. Further treatment was unnecessary, and subsequent doses of epidural morphine produced no recurrence of respiratory depression.

Discussion

Would Our Incidence of Complications Be Unacceptably High Compared With the More Traditional Use of Parenteral Opioids?

Minor complications were well within the previously published incidences (2–5). Reported incidences of respiratory depression vary from 0.33% (4) to 11% (5). We have now treated more than 100 additional patients with no further instances of delayed respiratory depression, making our incidence for the first 6 mo 1.9%, and to date, 0.7%. Although our sample size is relatively small, we believe we have shown the incidence to be acceptably low in our community practice.

Can Additional Systemically Administered Opioids Be Used With Epidural Morphine?

The administration of parenteral opioids in conjunction with epidural morphine remains controversial (1,5,6). Initial plasma morphine levels from epidural administration do not correlate well with pain relief

(7), and the development of early respiratory depression shows wide patient variability (8,9). Respiratory depression in the recovery room occurred in two patients who had had parenteral opioids as part of their operative anesthetic. Potential early respiratory depression in all postoperative patients dictates the high degree of monitoring in recovery rooms. Thus, we chose not to avoid parenteral opioids in our anesthetic regimen. In addition, the occasional delay in obtaining effective pain relief after reinjection of epidural morphine may result in an unacceptable level of pain. From the perspective of patient comfort, we found it sometimes necessary to administer small doses of morphine intravenously (1–2 mg) as a temporizing measure. There were no cases of either early or late clinical respiratory depression in such patients.

Can We Detect Delayed Respiratory Depression Using Clinical Criteria Without Special Monitors?

Respiratory depression occurs with both parenteral and epidural opioid administration but may not require treatment. Knill et al. (10) showed that nonsurgical volunteers receiving epidural morphine had more reduced minute ventilation, tidal volume, and CO₂ responses compared with patients given the same dose of morphine subcutaneously. Yet, even without surgical stimulation, no volunteers were reported to have required opioid reversal. Choi et al. (11) found no difference in the incidence of respiratory depression between patients given epidural or parenteral opioids. Catley et al. (12) administered intravenous morphine infusions for management of postoperative pain. In 10 patients, 456 episodes of pronounced oxygen desaturation (Spo₂ < 80%) occurred, accompanied by episodes of obstructive and central apnea. Similarly, no patients in either of these studies were reported to have required opioid reversal. Nurses customarily administer parenteral opioids and judge respiratory depression on clinical signs alone. However, it remains controversial whether patients receiving epidural opioids should be admitted to special care units (3,5,13,14), should have special monitors (5,10-12,15), or may be safely monitored outside special care units by trained nursing staff using clinical criteria for respiratory depression (1,6,16-18).

We believe the same standard of monitoring should be used for patients receiving epidural morphine as those receiving parenteral opioids. Because the delayed respiratory depression and accompanying somnolence from epidural morphine develop over a period of hours (1,10,11), there is ample time for early diagnosis and treatment. Effective monitoring for respiratory depression includes a close working relationship between the nursing staff and anesthesiologists and the timely availability and arrival of the on-call anesthesiologist when called.

Is There Additional Overall Risk Using Epidural Morphine Analgesia as Part of Postoperative Pain Management?

With precautions, our APS operates safely in a community practice without full-time in-house anesthesia coverage. Precautions include:

- 1. Cooperation of surgeons
- 2. Preprinted standardized epidural opioid orders
- 3. Tailoring dosages of epidural opioid to the minimum for effective pain relief
- 4. Administration of parenteral narcotics only on order of the anesthesiologist
- 5. Prior and continual in-servicing of nurses as to procedures and policies
- 6. Close, ongoing cooperation between nursing service and the anesthesiologists
- 7. Timely availability and arrival of the on-call anesthesiologist (within 30 min).

In summary, our incidence of complications was comparable to larger published studies. We have confirmed that delayed respiratory depression is a rare occurrence in the community practice setting. Clinical signs of respiratory depression used by properly trained floor nurses are acceptable monitors, and the timing of onset allows for treatment long before permanent sequelae occur. We hope our experience will encourage other anesthesiologists in small practices who may consider starting their own APS.

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Evaluation of the Effect of Perineuronal Morphine on the Quality of Postoperative Analgesia After Axillary Plexus Block: A Randomized Double-Blind Study

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RACZ H, GUNNING K, DELLA SANTA D, FORSTER A. Evaluation of the effect of perineuronal morphine on the quality of postoperative analgesia after axillary plexus block: a randomized double-blind study. Anesth Analg 1991;72:769–72.

A randomized, double-blind study was performed on 50 patients scheduled for elective hand and forearm surgery under axillary plexus block to evaluate the effect of perineuronal morphine on the quality of postoperative analgesia. Patients were divided into two groups. In group A (n=25)5 mg of preservative-free morphine in 1.0 mL of 0.9% saline was added to the local anesthetic solution (20 mL of 1% plain lignocaine, 20 mL of 0.5% plain bupivacaine). They

also received an intramuscular placebo injection of 1.0 mL of 0.9% saline in the upper thigh. In group B (n=25), 1.0 mL of 0.9% saline was added to the local anesthetic solution and patients received an intramuscular injection of 5 mg of preservative-free morphine in 1.0 mL of 0.9% saline in the thigh. The addition of morphine to the local anesthetic solution for the axillary block did not shorten the onset time of the block, improve the quality of postoperative pain relief, or provide longer lasting analgesia than that obtained with intramuscular morphine.

Key Words: ANALGESICS, MORPHINE.
ANESTHETIC TECHNIQUES, REGIONAL—axillary plexus block.

Morphine is routinely administered by intramuscular, intrathecal, or epidural routes for the relief of pain. It is thought to produce its effects by an action on specific receptors in the dorsal horn of the spinal cord and on central opioid receptors (1). Recent reports have suggested that morphine injected perineurally in patients with chronic pain may also have a clinically significant effect and that its duration of action may be longer than that of systemically administered morphine or bupivacaine (2). Sanchez et al. (3) proposed the neuroaxonal transport of morphine to the spinal cord as an explanation for this effect. Other mechanisms that have been put forward are a localanesthetic-like action (4) or a direct effect of morphine on stereospecific opioid receptors on the cell membrane of peripheral nerve axons (5).

Other investigators (6,7), however, have failed to

demonstrate any significant analgesic effect of morphine administered perineurally.

The present randomized double-blind study was therefore performed to evaluate whether morphine administered perineurally with a local anesthetic solution could influence the onset time of the block or the duration or quality of postoperative analgesia when compared with a similar dose of morphine injected systemically.

Methods

Fifty patients (ASA physical status I or II), aged 16–75 yr, undergoing minor orthopedic surgery on the hand and forearm under axillary plexus block were included in the study.

The study was approved by the hospital ethics committee, and informed consent was obtained from all patients in the study. Patients with a diagnosis of, or at risk from, a peripheral neuropathy, and patients regularly taking analgesics or psychotropic drugs, or incapable of adequate communication, were excluded from the trial. The patients were instructed preoper-

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atively in the use of a 10-point visual analogue scale for pain evaluation.

Patients were randomly assigned to two groups, A (n = 25) and B (n = 25). In a double-blind manner, group A patients received 5 mg of preservative-free morphine in 1.0 mL of 0.9% saline, which was added to 40 mL of a standard local anesthetic solution (20 mL of 1% plain lignocaine, 20 mL of 0.5% plain bupivacaine). At the same time they were given an intramuscular injection of 1.0 mL of 0.9% saline in the opposite thigh. Patients in group B received 1.0 mL of 0.9% saline with the local anesthetic solution and an intramuscular injection of 5 mg of preservative-free morphine in the contralateral thigh. The dose of morphine was chosen after a review of the literature (2,3,6).

All axillary plexus blocks were performed using the same technique by an experienced anesthesiologist. The arm was supinated and abducted to 90°. Using a 23-gauge Top Pole insulated needle and with the aid of a nerve stimulator, the median, ulnar, radial, and musculocutaneous nerves were accurately located using a current of <1 mA, and 10 mL of local anesthetic solution was injected around each nerve. The time at which the block was sufficient for surgery was recorded, and sensory and motor blocks were evaluated immediately before surgery. Sensory block was evaluated by pinprick. Motor block was evaluated using a four-point scale (0 = full motor power;1 = decreased motor power but still able to move arm; 2 = unable to move arm but able to move fingers; 3 = complete motor block). Intensity of postoperative pain was evaluated using a visual linear analogue scale from 0 (no pain) to 10 (the worst pain imaginable). Pain intensity and sensory and motor block were evaluated immediately postoperatively, 1 and 2 h later, and again before discharge home or to the ward. At the time of discharge the patients were given a questionnaire with visual analogue scales and asked to evaluate their postoperative pain intensity. They were provided with a supply of analgesics (400 mg pirprofen and 220 mg propyphenazone). Patients were asked to record the time they noticed the first postoperative pain and the intensity of the pain. They were then asked to score the pain at hourly intervals and the time and intensity of pain when they first needed to take an analgesic. The total number of tablets of each analgesic taken was recorded. The patients were interviewed 24 h postoperatively, when an evaluation of pain was performed, and the quality of appetite, sleep, and the presence of subjective secondary effects of opioid anesthetics during the first postoperative 24 h was recorded.

<u>Table 1</u>. Comparison of Groups: Demography and Type of Surgery

	Group A	Group B
No. of patients	19	21
Men/women	13/6	17/4
Age (yr)	38 ± 16	36 ± 14
Weight (kg)	72 ± 12	70 ± 10
Height (cm)	174 ± 9	171 ± 8
Hospitalized/outpatients	2/17	10/12
Type of operation		
Soft tissue	9	11
Bone	10	10
Duration of operation (min)	84 ± 37	92 ± 63

Values for age, weight, height, and duration of operation are expressed as mean \pm sp.

An unpaired two-tailed Student's t-test was used to compare parametric data, and a Wilcoxon two-sample test was used to compare the visual analogue scales. A probability value of less than 0.05 was considered significant. Ordinal data are presented as medians with ranges; interval data are presented as mean \pm SEM.

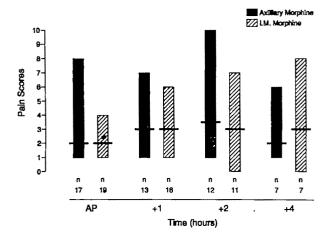
Results

Ten patients were excluded from the analysis because of protocol violations. Patient data, type, and duration of operation are shown in Table 1. The time of onset of the blocks sufficient for surgery was 36 ± 3 min in group A and 30 ± 3 min in group B (not a significant difference). However, in one patient in each group it was not possible to obtain adequate anesthesia and the blocks were supplemented with either nitrous oxide or local infiltration with 1% lidocaine. These patients were not excluded from the analysis.

The duration of the motor block was 532 ± 37 min in group A and 644 ± 68 min in group B. Sensory block lasted 496 ± 42 min in group A and 596 ± 61 min in group B. The mean time at which pain first appeared was 480 ± 42 min in group A and 478 ± 41 min in group B.

The time at which analgesia was first required was 646 ± 58 min in group A and 661 ± 62 min in group B. There was no significant difference between the groups. The median pain score at the first appearance of pain was 2 (range, 1–8) in group A and 2 (range, 1–4) in group B. The evolution of pain scores for the first hours after the appearance of pain is shown in Figure 1.

The type of operation had no influence on the intensity of postoperative pain. There was no signif-



<u>Figure 1</u>. Postoperative pain scores (VAS), presented using medians (horizontal bars) and ranges (vertical columns), for the first 4 h after the first appearance of pain (AP). Patients were excluded from the analysis after they required supplementary analgesia, which explains the decreasing number of patients during the follow-up. There was no significant difference between the groups for the time of appearance of first pain, or for the pain scores between the two groups.

Table 2. Side Effects

	Group A	Group B
Nausea	1	0
Vomiting	1	4
Stomach ache	1	0
Dysphoria	1	3
Urinary retention	0	0
Urticaria	0	0

One patient of each group showed an erythema at the site of injection.

icant difference between the groups with regard to the time at which the first analgesic was taken or the total number of analgesics taken. Eleven patients, five in group A and six in group B, did not have sufficient pain to require any analgesia. The time to return of motor power and sensation was similar in both groups. Fifteen patients complained of poor sleep secondary to pain (seven in group A and eight in group B).

There was no difference between the groups regarding systemic secondary effects of morphine (Table 2).

Discussion

Our results suggest that 5 mg of morphine when added to the local anesthetic solution for an axillary plexus block does not alter the time of onset of the block or provide prolonged postoperative analgesia when compared with a similar dose of morphine given intramuscularly.

In contrast, in a study comparing the effects of 3 μg/kg perineural buprenorphine and 50 μg/kg morphine, "satisfactory" postoperative pain relief of 18 and 35 h was obtained with morphine and buprenorphine, respectively (8). This study did not include an intramuscular control group, and therefore there was no comparison as to the effect of morphine administered in various ways in this group of surgical patients. A supraclavicular technique was also used in this study. Opioids injected perineurally could diffuse from the brachial plexus sheath into the epidural space and react with opioid receptors in the substancia gelatinosa of the dorsal horn. This may be more likely after a supraclavicular approach than after an axillary approach to the brachial plexus. Gobeaux et al. (9) reported a longer duration of postoperative analgesia when 100 mg of meperidine was added to the local anesthetic solution for an axillary plexus block. However, they did not have an intramuscular control group in the study, and their results could be explained by systemic absorption of the meperidine. According to the results of previous studies, the duration of action of perineuronal opioids is greater than 10 h (2,3,8,9). Our mixture of bupivacaine and lignocaine used for the axillary block might have obscured any initial effect of the opioids; however, if perineuronal morphine is of value in improving the quality of postoperative analgesia, its duration of action should be longer than that of the axillary block. From the results it can be seen that the first appearance of pain corresponds to the offset time of the block in the two groups, and we were unable to demonstrate any prolonged action of morphine administered perineurally.

Mays et al. (2) obtained pain relief lasting up to 24 h in patients with chronic pain when they blocked the brachial plexus with 6 mg of morphine in 30 mL of saline. They suggested that this could be explained by an increase in the refractory period of the axon or by axonal uptake and transport of morphine to the spinal cord.

Studies of the action of opiates on primary afferent fibers have produced conflicting results. Jurna and Grossmann (10) reported increased $A\beta$ and decreased $A\alpha$ and C-fiber components of the compound action potential with intravenous morphine. Frank and Sunha (11) found stereospecific opioid receptors on the intracellular surface of peripheral nerve axons, but noted that enkephalins could not reach these receptors in effective concentrations from the extracellular fluid. A weak local anesthetic type of action on peripheral nerves has been demonstrated with fen-

tanyl (4). This effect was found only on desheathed nerves, and thus it is unlikely that opioids would diffuse through a peripheral nerve sheath sufficiently to affect conduction. No effects were found when preservative-free morphine was applied directly to peripheral nerves (12).

Our results are in agreement with other studies performed on patients with acute pain (6,7), where perineuronal injection of morphine did not provide pain relief. The difference in the nature of transmission of acute and chronic pain may account for these differing results.

In conclusion, we can find no evidence that 5 mg of morphine administered perineurally has a prolonged duration of action when used in the management of postoperative pain after minor surgery, compared with 5 mg of morphine administered intramuscularly, or that it improves the quality of postoperative analgesia compared with that provided by an axillary block performed with a local anesthetic solution of lignocaine and bupivacaine. The systemic absorption of the drug may explain any analgesic effect.

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Effect of pH of Bupivacaine on Duration of Repeated Sciatic Nerve Blocks in the Albino Rat

Carol E. Baker, BS, R. Lee Berry, BGS, Robert C. Elston, PhD, and The Local Anesthetics for Neuralgia Study Group

BAKER CE, BERRY RL, ELSTON RC, THE LOCAL ANESTHETICS FOR NEURALGIA STUDY GROUP. Effect of pH of bupivacaine on duration of repeated sciatic nerve blocks in the albino rat. Anesth Analg 1991;72:773–8.

Tachyphylaxis has been ascribed to tissue acidification after repeated injections of acidic local anesthetic solutions. We studied the effect of pH on the duration of action of bupivacaine to determine the validity of this proposed mechanism of tachyphylaxis by injecting bupivacaine solutions adjusted to pH 4.2 or 6.8 into a surgically implanted

system created to permit in vivo irrigation of rat sciatic nerves with local anesthetic. Tachyphylaxis developed at both pH values. The results fail to support the acidification hypothesis as there was no statistically significant effect of a 400-fold difference in hydrogen ion concentration on the development of tachyphylaxis or the duration of motor dysfunction.

Kew Words: ANESTHETICS, LOCAL—bupivacaine. PHARMACOLOGY, TACHYPHYLAXIS—bupivacaine.

Local anesthetic tachyphylaxis has been described in in vivo (1–3) but not in in vitro (4) peripheral nerve preparations. Hypotheses as to the mechanism of local anesthetic tachyphylaxis fall into two categories: pharmacokinetic (less drug reaches the sodium channel) and pharmacodynamic (the sodium channel becomes resistant to the same concentration of local anesthetic drug). One pharmacokinetic hypothesis proposed to explain local anesthetic tachyphylaxis is progressive tissue acidification from repeated injections of (acidic) commercial solutions of local anesthetics resulting in decreasing percentages of injected drug penetrating the nerve. This hypothesis is based on the inverse relationship between the concentration of hydrogen ions and the concentration of the basic (uncharged and presumably more active or more diffusible) species of local anesthetic molecule in aqueous solution (5).

The use of a surgically implanted system for repeated nerve blocks consisting of a perineural silicone cuff connected through a small tube to an externalized injection port was recently described by Kroin et al. (6). The system, once implanted, permitted repeated administration of local anesthetic solutions to a segment of peripheral nerve with a reproducibility and lack of perineural needle trauma not possible with repeated conventional peripheral nerve blocks. We modified the system of Kroin et al. by making it totally implantable and by changing the relatively stiff perineural cuff to a membranous silicone sheath. Using this system, we studied the effect of the pH of the bupivacaine solution on the development of local anesthetic tachyphylaxis.

Methods

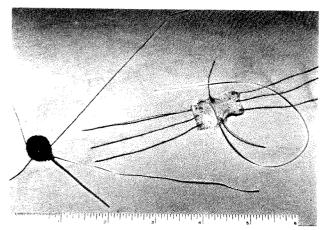
Animal Model

Ten healthy male albino rats of various ages weighing 450–600 g were used in a study approved by the Institutional Animal Care and Use Committee of the Louisiana State University Medical Center. Ten other animals had surgical implantation of the experimental system described below but did not participate in this phase of the project because of intraoperative nerve injury (4 animals), postoperative pneumonia (1), wound infection (2), wound dehiscence (1), in-

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<u>Figure 1</u>. Surgically implantable peripheral nerve irrigation system. Injection port (*left*), nerve sheath with attached interconnecting tubing (*right*). (Scale in inches.)

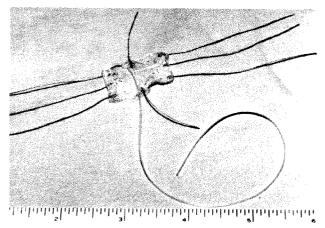


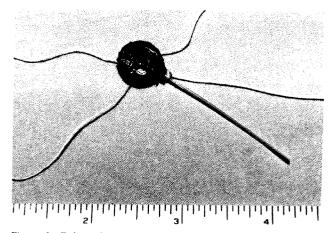
Figure 2. Enlarged view of nerve sheath. (Scale in inches.)

correct surgical implantation of system (1), and anesthetic death (1).

The implanted peripheral nerve irrigation system consisted of three components: an injection port, a segment of interconnecting silicone tubing, and a membranous silicone nerve sheath (6–14) (Figures 1–3). The components were handmade and were autoclaved before implantation. The sheath was positioned around a sciatic nerve and was connected with the tubing to the subcutaneous injection port. (See Appendix for detailed description of manufacture and implantation.)

Injections and Collection of Data

Commercial solutions of 0.25% bupivacaine (Sensorcaine, Astra Pharmaceuticals, Westboro, Mass.;

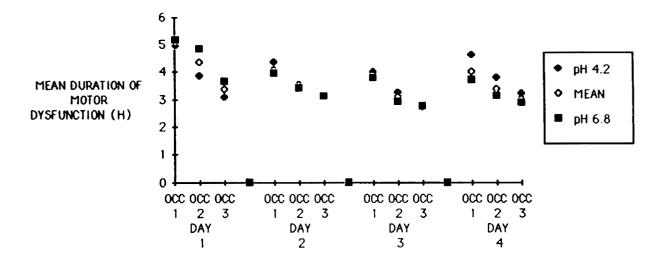


<u>Figure 3</u>. Enlarged view of injection port. (Scale in inches.)

supplied courtesy of the local Astra distributor) were adjusted to pH 4.2 or 6.8 by adding 0.1 N HCl or 0.1 N NaOH, respectively. The pH was measured with a color indicator paper (Indicator Strips, American Scientific Products, McGraw Park, Ill.).

Animals received 0.3-mL injections of 0.25% bupi-vacaine through the injection ports from a 1-mL syringe connected to a 30-gauge needle through an extension tube consisting of a 40- to 60-mm-long silicone tube (outside diameter [OD], 0.6 mm) fitted with Luer male and female adapters on each end. The injection apparatus was a miniature version of the "immobile needle" apparatus originally described by Winnie (15). Its use allowed the animals to move freely during the time required for the injection.

At the beginning of each test day, all injections were performed within minutes of each other. The drug effect on the animal's sciatic nerve was verified by measuring the hind limb motor dysfunction on the side of the sciatic nerve sheath, and the duration of drug effect was measured by observing each animal's gait at 15-min intervals. Once hind limb function seemed grossly symmetrical, the animal was placed on a smooth surface and observed while gentle traction was manually applied to his tail. This elicited a gripping reflex by his hind toes allowing detection of subtle degrees of residual drug effect (16). Local anesthetic duration was measured as the time (in hours) from injection to that when the function of the operated hind extremity was equal to the function of the contralateral hind limb. Animals received their second and third injections on a test day after two consecutive evaluations of the prior injections' effect demonstrated equal motor function of both hind extremities.



The time interval between the date of operation and the sequence of injections described varied from 1 to 12 wk. Animals had had between one and nine previous local anesthetic injections through their implanted systems at least 3 days before their participation in this study.

Design

Animals received injections of bupivacaine solutions (pH 4.2 or 6.8) on three occasions on each of four consecutive test days. On each test day, all three injections for any one animal had the same pH. The pH of the bupivacaine solution injected on any test day was determined on the basis of random assignment of the animals into one of four groups: group A (3 animals) always received bupivacaine with pH 4.2, group B (3 animals) always received bupivacaine with pH 6.8, groups C and D (2 animals each) received bupivacaine solutions of a different pH on different days according to a four-period crossover design (pH 4.2, 6.8, 4.2, 6.8 for group C and pH 6.8, 4.2, 6.8, 4.2 for group D).

The effects of the three variables (occasion, test day, and pH) on local anesthetic duration, expressed in hours of observed drug effect, were analyzed statistically using a linear analysis of variance model in which rats were considered as blocks. Statistical tests for interactions between these variables were also performed. A specific analysis of covariance for a carryover effect was performed to ensure that the effect of any injection was not influenced by the pH of the previously injected solution. Differences were judged to be statistically significant if P < 0.05.

<u>Figure 4</u>. Mean hind limb motor dysfunction duration on three occasions each day for four consecutive days (adjusted for rat effects, treated as blocks) [n = 10, 5 at pH 4.2, 5 at pH 6.8, and mean of all 10].

Results

The statistically significant effect of occasion, the tachyphylaxis variable, is illustrated in Figure 4 (also Table 1) by the declining duration of successive doses of bupivacaine within each of the 4 days. The effect of test day was also statistically significant; the mean duration of all bupivacaine injections on test day 1 was longer than on test days 2, 3, and 4. However, the mean duration of motor dysfunction on test days 2 through 4 was not significantly different. The statistically significant occasion × test day interaction demonstrates a more pronounced development of tachyphylaxis within test day 1 than within test days 2, 3, and 4. The pH of the bupivacaine solution had no effect on either the development of tachyphylaxis (occasion × pH interaction) or the duration of motor dysfunction. There was no significant carryover effect from a prior injection of bupivacaine solution of a different pH.

Discussion

The peripheral nerve irrigation systems implanted into the 10 animals used in this study performed well. Repeated injections of bupivacaine resulted in progressively decreased duration of drug action. Thus, tachyphylaxis did develop. The lack of a statistically significant effect of a 400-fold difference in solution hydrogen ion concentration (95% confidence limits,

Table 1. Mean Duration in Hours of Motor Dysfunction

Test day	Occasion	pH 4.2 (n = 5)		pH 6.8 (n = 5)		Mean
		Mean	SEM	Mean	SEM	(n=10)
1	1	4.99	0.20	5.17	0.20	5.08*
	2	3.89	0.20	4.87	0.20	4.38
	3	3.09	0.20	3.67	0.20	3.38
2	1	4.35	0.22	3.94	0.18	4.07
	2	3.54	0.22	3.44	0.18	3.45
	3	3.10	0.22	. 3.15	0.18	3.11
3	1	3.99	0.20	3. <i>7</i> 7	0.20	3.88
	2	3.24	0.20	2.92	0.20	3.08
	3	2.74	0.20	2.77	0.20	2.76
4	1	4.60	0.22	3.69	0.18	4.01
	2	3.79	0.22	3.15	0.18	3.37
	3	3.23	0.22	2.90	0.18	3.00

[&]quot;The SEM for any one occasion, on any one day (mean of all 10 rats) is = 0.19 h (95% confidence limits from the analysis of variance model).

-0.2 to +0.5 h) on the duration of motor dysfunction caused by bupivacaine local anesthetic blockade and the lack of a statistically significant difference in tachyphylaxis development owing to the pH of the solution fail to support the hypothesis that peripheral nerve acidification inhibits bupivacaine-induced neural blockade in the intact sciatic nerves of living rats.

Of further interest in the mechanism of tachyphylaxis is the above-mentioned phenomenon's occurring despite mechanical separation of the sciatic nerve from the surrounding muscles with a silicone sheath. If this sheath formed an effective diffusion barrier between the contained segment of the nerve and the surrounding nonneural tissue, then tachyphylaxis may be due to events within the nerve itself and may not be dependent on changes (e.g., increased blood flow) occurring in its environment. If increased local blood flow is an important determinant of local anesthetic tachyphylaxis as has been hypothesized (17), this may mean that changes in intraneural blood flow are the important factors. However, other pharmacokinetic mechanisms such as neural edema (18) and progressively greater leakage of injected bupivacaine from the sheath with successive injections cannot be excluded as mechanisms of the tachyphylaxis observed. Residual local anesthetic effect undetectable by gross inspection before the second and third injections within each day is another possibility that must be considered.

The reason for the statistically significantly longer duration of local anesthetic injections on test day 1 as compared with test days 2, 3, and 4 is unclear. The mechanism of this effect may be the same as the tachyphylaxis effect or may be unrelated.

An implantable system consisting of a subcutaneous injection port leading to a specific nerve might have clinical utility in the management of some neuralgias provided that (a) the system remains patent, (b) local anesthetic drug efficacy is not significantly attenuated over time, and (c) complications of the operative procedure (immediate nerve injury, surgical infection, chronic nerve irritation) and the indwelling system are few or minor. It is not known for how many months or years injections of local anesthetic solutions into such a system will effectively block an ensheathed nerve. (Local anesthetic injections made into the implantable systems of some of the study animals continued to produce motor dysfunction for up to 13 mo after surgical implantation.) Neurolytic drugs could presumably be injected through such a system implanted in a patient with a chronic neuralgia or with muscle spasticity. Also, the effects of solutions of substances such as neurotrophic factors could be studied using a peripheral nerve irrigation system of the type described.

In conclusion, tachyphylaxis developed to the effects of bupivacaine solutions adjusted to pH 4.2 or 6.8 injected into a surgically implanted system designed to permit in vivo irrigation of rat sciatic nerves with local anesthetic drugs. There was no statistically significant effect of pH on duration of drug effect or on development of tachyphylaxis, which fails to support the hypothesis that tissue acidification is an important mechanism of this phenomenon.

An implantable system for irrigation of peripheral nerves with local anesthetic drugs may have clinical utility in the management of some chronic neuralgias and spastic conditions provided certain problems observed with the present system can be avoided or minimized.

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Appendix

Manufacture and Implantation of Nerve Irrigation System

Injection Port

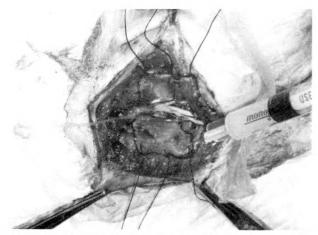
The injection port was fashioned from a blood-collecting glass tube with a 10.5-mm OD (Vacutainer, Becton-Dickinson, Rutherford, N.J.). Both the glass tube and the rubber stopper were cut down to keep the height of the injection port less than 9 mm. A 1-mm hole was drilled in the side of the port near the base, and a 15-mm-long, 0.9-mm-OD silicone tubing (Silastic, Dow-Corning, Midland, Mich.) was inserted 1 mm into the glass tube. The tubing was secured in place with a medical-grade silicone adhesive (Medical Grade A Silicone Adhesive, Dow-Corning; RTV-A) that was vulcanized at room temperature. The entire port was coated in RTV-A to smooth the port's contour and to prevent direct contact between the animal's subcutaneous tissues and the port's rubber and glass.

Nerve Sheath and Interconnecting Tubing

A membranous nerve sheath (7,8) was used rather than the thicker preformed silicone cuff used by previous investigators (6,9–14) to minimize the nerve damage that typically results from long-term implantation of such cuffs. The sheath was constructed from 0.025-mm-thick silicone membrane (General Electric Company Membrane Products Division, Schenectady, N.Y.) (7,8) reinforced along the perimeter with RTV-A injected through a 27-gauge needle. Polyester sewing threads were attached with RTV-A to help in maneuvering the sheath under the nerve and to anchor the sheath, once wrapped around the nerve, to the fascia underlying it. A piece of 0.6-mm-OD silicone tubing (Silastic), of sufficient length to connect the injection port with the sheath, was affixed to the inside surface of the sheath using RTV-A.

Implantation

General anesthesia was induced and was maintained throughout the operative procedure. One thigh and the skin area just caudad to the scapulae were shaved. The surgical field was then prepared and was draped in a sterile fashion. Kanamycin (5 mg/kg) was administered intramuscularly approximately 30 min before the first skin incision was made. The sheath was positioned under a 1-cm segment of the animal's sciatic nerve that had been exposed through a lateral thigh incision (Figure 5). The sheath was then folded around the nerve, and the contiguous edges were glued together with RTV-A. The threads, originally on each side of the membrane having been approximated after folding, were then tied together, and the free strands were sutured to the underlying fascia. This was done to prevent the sheath from moving from its original position during postoperative locomotion. A second transverse incision was made on the rat's dorsal skin just caudad to the scapulae (to avoid interference with locomotion), and a surgical



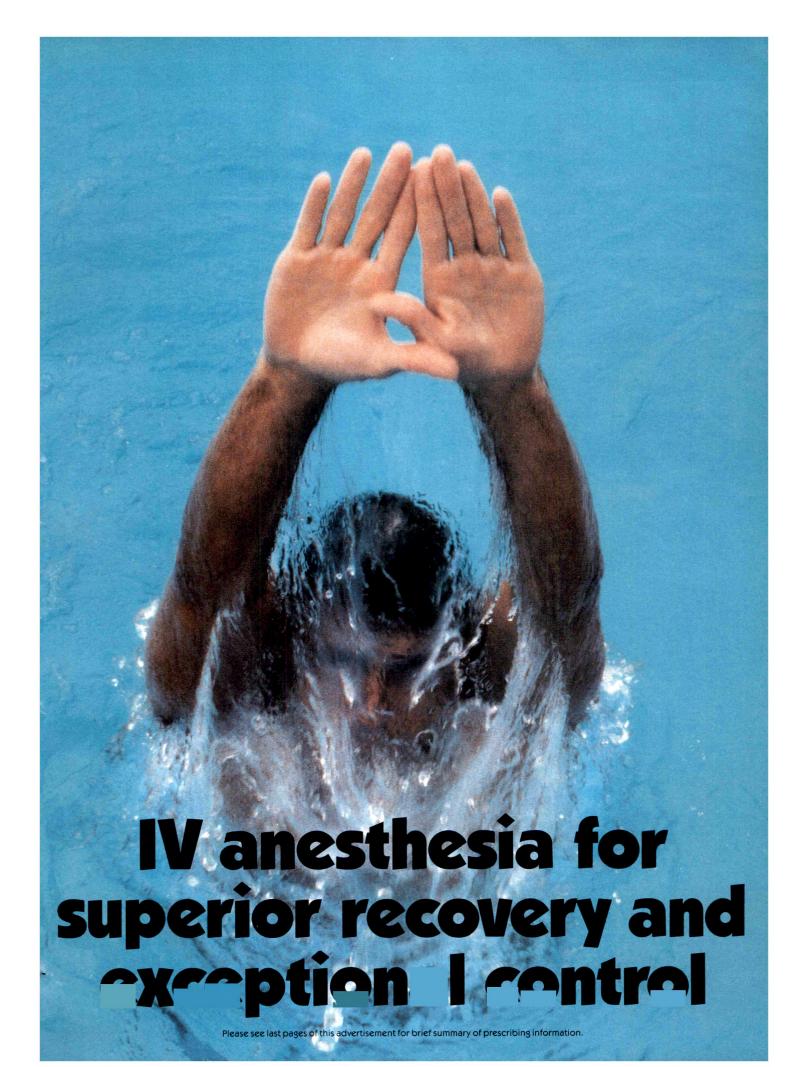
<u>Figure 5</u>. View of surgical dissection of rat's left sciatic nerve with silicone membrane beneath nerve. The membrane will be folded over the nerve to form the sheath.

pocket was created in the subcutaneous tissue. The interconnecting tubing was threaded from the sheath through the gluteal muscles to the subcutaneous layer of the thigh and then cephalad to the pocket created for the injection port. The ends of the tubing were then connected. Next, the polyester threads attached to the base of the port were sutured to the deep fascia of the back. The system was then tested for patency and continuity, and the incisions were closed with sutures and staples.

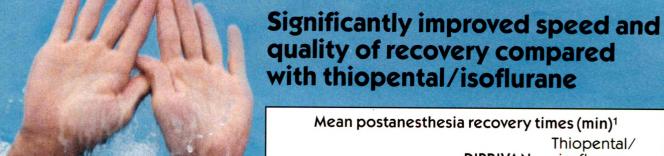
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Mean postanesthesia recovery times (min) ¹		
	DIPRIVAN	Thiopental/ isoflurane
Duration of anesthesia	85*	57
Response to commands	3.5*	6.1
Fully oriented	5.5	9.4
Able to tolerate fluids	61*	130
"Ready" for discharge	138*	206

-adapted from Korttila et al, p A5641

 Majority of patients are generally awake, responsive, and oriented within 8 minutes

Statistically significant (P < .05). Measurements taken from time of discontinuation of all maintenance anesthesia.

recovery and anesthetic control

Significantly less nausea and vomiting than with thiopental/isoflurane

	DIPRIVAN	Thiopental/ isoflurane
Wetchler ²	(n = 20)	(n = 20)
Nausea/vomiting	20%	65%
Sung et al ³	(n = 49)	(n = 50)
Nausea/vomiting	8.1%	30%

As part of a balanced anesthetic technique, DIPRIVAN is a cost-effective alternative to thiopental/isoflurane for induction and maintenance.

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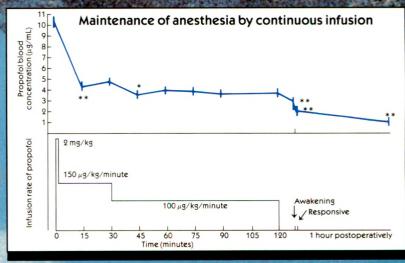
For induction and maintenance





Maintenance of anesthesia as easily controlled as with isoflurane

■ Steady state blood concentrations are proportional to rate of administration



-adapted from Herregods et al, p 3644

*Significant difference (P< .05) from previous value. **P< .02. (Mean and SEM values are shown.)

After a loading dose of 2 mg/kg, anesthesia was maintained with 150 μ g/kg/min for 30 minutes—then 100 μ g/kg/min for 90 minutes.⁴

■ Total body clearance exceeds estimates of hepatic blood flow⁵

No active metabolites produced

As with most anesthetic agents, clearance rate of DIPRIVAN decreases in elderly patients.

ecover, and anesthetic control

Hemodynamic effects are controllable and dose-dependent

- Blood pressure (BP) predictably decreases on induction (sometimes > 30%) but is within acceptable ranges for healthy individuals*
- Hemodynamic effects during induction are generally more pronounced than with traditional IV induction agents

After initial decreases in BP following induction, hemodynamics return toward baseline

The cardiovascular effects of DIPRIVAN may be increased in patients who have received sedative or narcotic premedications.

Strict aseptic techniques must always be maintained while handling DIPRIVAN. DIPRIVAN is a single-use parenteral product and contains no antimicrobial preservatives. DIPRIVAN Injection should be prepared for use just prior to initiation of each individual anesthetic procedure. DIPRIVAN Injection should be drawn into sterile syringes immediately after ampules are opened. Administration should commence promptly and be completed within 6 hours after the ampules have been opened.

*Elderly, debilitated, and/or hypovolemic patients, and those rated ASA III/IV, may have more profound adverse Induction dose requirements may be reduced

Please see last pages of this advertisement for brief summary of prescribing information.

For induction and maintenance





Superior recovery and exceptional anesthetic control

As part of a balanced anesthetic technique, DIPRIVAN is a cost-effective alternative to thiopental/isoflurane for induction and maintenance.

Significantly improved speed and quality of recovery compared with thiopental/isoflurane

Significantly less nausea and vomiting than with thiopental/isoflurane

 As convenient and as easily controlled as isoflurane for maintenance of anesthesia

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(For full prescribing information, see package insert.)

INDICATIONS AND USAGE: DIPRIVAN Injection is an IV anesthetic agent that can be used for both induction and/or maintenance of anesthesia as part of a balanced anesthetic technique for inpatient and outpatient surgery. DIPRIVAN Injection is not recommended for obstetrics, including cesarean section deliveries, because there are insufficient data to support its safety to the fetus. (See PRECAUTIONS) DIPRIVAN Injection is not recommended for use in nursing mothers because DIPRIVAN Injection has been reported to be excreted in human milk and the effects of oral absorption of small amounts of proportion are not known. (See PRECAUTIONS) DIPRIVAN Injection is not recommended for use in prediction in the proportion of the pro **EMULSION FOR IV ADMINISTRATION** Patients should be continuously monitored for early signs of significant hypotension and/or bradycardia. Treatment may include increasing the rate of intravenous fulid, elevation of lower extremities, use of pressor agents, administration of atropine. Apnea often occurs during induction and may persist for more than 60 seconds. Ventilatory support may be required. Because DIPRIVAN injection is an emulsion, caution should be exercised Patients should be continuously monitored for early signs of significant hypotension and/or pracycardia. Ireatment may include increasing the rate of intravenous fluid, elevation of lower extremities, use of pressor agents, or administration of atropine. Apnea often occurs during induction and may persist for more than 60 seconds. Ventilatory support may be required. Because DPRIVAN injection is an emulsion, caution should be exercised in patients with disorders of lipid metabolism such as primary hyperipoproteinemia, diabetic hyperipemia, and pancreatitis. Since DPRIVAN injection is never used atone, an adequate period of evaluation of the awakend patient is indicated to ensure satisfactory recovery from general anesthesia prior to discharge of the patient from the recovery room or to home. Transient local pain may occur during intravenous sinjection, which may be reduced by prior injection of IV lidocaine (1 0 m.l. of a 1% solution). Venous sequelae (phiebitis or thrombosis) have been reported rarely (< 1 %). In two well-controlled clinical studies using dedicated intravenous carbeters, no instances of venous sequelae were reported rurely to 14 days following induction. Pain can be minimized if the larger veins of the torearm or antecubital fossa are used. Accidental crinical extravasation and intentional injection into subcutaneous or pervascular lissues of animals caused minimal bissue reaction. Intra-arterial injection in amount and induction administration and induction and patients. Accidental intra-arterial injection has been reported in a patient, and other than pain, there were no major sequelae. Perioperative myocionia, rarely including opisthotionus, has occurred in a temporal relationship in cases in which DIPRIVAN injection has been administrated. Clinical features of anaphytaxis, which may include bronchospasm, erythema, and hypotension, occur arely following DIPRIVAN injection administration, although use of other drugs in most instances makes the relationship to DIPRIVAN injection administratio for use in nursing mothers because DIPHIVAN has been reported to be excreted in human milk and the effect of or al absorption of small amounts of propotol are not known. Pediatric Use: DIPRIVAN lighterion is not recommended for use in pediatric patients because safety and effectiveness have not been established. Neurosungical Anesthesais: Studies to date indicate that DIPRIVAN linjection decreases cerebral blood flow, cerebral metabolic oxygen consumption, and intracranial pressure, and increases cerebrovascular resistance. DIPRIVAN linjection does not seem to affect cerebrovascular reactivity to changes in arterial carbon dioxide tension. Despital these findings, DIPRIVAN linjection is not recommended for use at this time in patients with increased intracranial pressure or impaired cerebral circulation because DIPRIVAN linjection may cause substantial decreases in arterial pressure, and consequently, substantial decreases in cerebral perfusion pressure. Further studies are needed to substantiate what happens to intracranial pressure following DIPRIVAN linjection when decreases in mean atterial and cerebral perfusion pressures are presented by anonymist measure. Annesse extremes a training and cerebral perfusion pressures are presented by anonymist measure. arderial pressure, and consequently, substantial decreases in cerebral perfusion pressure. Further studies are needed to substantiate what happens to intracranial pressure following DIPRIVAN Injection when decreases in mean arterial and cerebral perfusion pressures are prevented by appropriate measures. ADVERSE REACTIONS, Adverse event information is derived from controlled clinical trials and worldwide marketing experience. In the description below, rates of the more common events represent US/Canadian clinical study results. Less frequent events are derived principally from marketing experience in approximately 7 million patients and from publications there are insofficient data to support an accurate estimate of their incidence rates. The following estimates of adverse events for DiPRIVAN Injection are derived from reports of 1573 patients included in the US/Canadian induction and maintenance studies. These studies were conducted using a variety of premedicants, varying lengths of surgical procedures and various other anesthetic agents. Most adverse events were mild and transient. The following adverse events were reported in patients treated with DIPRIVAN Injection. They are presented within each body system in order of decreasing frequency. Incidence Greater than 1% – All events regardless of causality, derived from clinical trials. Body as a Whole: Fever Cardiovascular Hypotension' (see also CLINICA) PHARMACOLOGY). Bradycardia. Hypotension' (see also CLINICA) PHARMACOLOGY). Bradycardia. Hypotension' (see also CLINICAL PHARMACOLOGY). Bradycardia Hypotension' (see also CLINICAL PHARMACOLOGY). Bradycardia Hypotension' (see also CLINICAL PHARMACOLOGY). Bradymoness, Coldness, Respirationship Probable (Adverse events reported only in the literature, not seen in clinical trials, are italicized.) Body as a Whole: Extremities Pain, Chest Pain, Neck Stiffness, Trunk Pain. Cardiovascular: Tachycardia, Premature Ventriculis.
Extremities Pain, Chest Pain, Neck Stiffness, Trunk Pain. Cardiovascular: Tachycardia, Premat

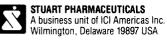
DIPRIVAN® (propofol) Injection

Injection Site: Discomfort, Phiebitis, Hives/liching, Redness/Discoloration, Musculoskeletal: Myalgia Respiratory: Upper Airway Obstruction, Bronchospasm, Dyspnea, Wheezing, Hypoventilation, Burning in Throat, Snezing, Tachypnea, Hyperventilation, Hypoxia, Skin and Appendages; Rash, Urticaria. Special Senses: Ambiyopia, Diplopia, Eye Pain, Isate Perversion, Tinnitus Urogenital: Urine Retention, Green Urine, Incidence Less than 194 — Causal Relationship Unknown (Adverse veveter reported only in the literature, not seni in clinical trials, are Italicized.) Cardiovascular: Arrhythmia, Bigeminy, Edema, Ventricular Fibrillation, Heart Block Myocardialischemia. Central Nervous System: Anxiety Emotional Lability, Depression, Hysteria, Insormia, Generalized and Localized Seizures, Opisthotonus. Digestive: Diarrhea. Respiratory: Laryngospasm. Skin and Appendages: Diaphoresis. Pruritus, Conjunctival Hyperemia. Special Senses: Ear Pain, Nystagmus. Urogenital: Abnormal Urine. DRUG ABUSE AND DEPENDENCE: None known OVERDOSAGE: To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. If accidental overdosage occurs. DIPRIVAN Injection administration should be discontinued immediately. Overdosage is likely to cause cardiorespiratory depression. Respiratory depression should be treated by artificial ventilation with oxygen. Cardiovascular depression may require repositioning of the patient by raising the patient: Induction: Dosage should be individualized and titrated to the desired effect according to the patients age and clinical status. Most adult patients under 55 years of age and classified ASA I and II are likely to require? 20 to 2.5 mg/kg of DIPRIVAN Injection, for induction when unpremedicated or when premedicated vide nor abenzodiazepines or intramuscular nacrotics. For induction. DIPRIVAN Injection should be titrated (approximately 40 mg every 10 seconds) against the response of the patient until the clinical signs show the onset of anesthesia not controlled after a five-minute period, other means such as a narcotic, barbiturate, vasodilator, or inhalation agent therapy should be initiated to control these responses. For minor surgical procedures (ie. body surface) 60%-70% nitrous oxide can be combined with a variable rate DIPRIVAN Injection infusion to provide satisfactory anesthesia. With more stimulating surgical procedures (ie. intra-abdominal) supplementation with analgest agents should be considered to provide a satisfactory anesthetic and recovery profile Infusion rates should always be titrated downward in the absence of clinical signs of light anesthesia until a mild response to surgical stimulation is obtained in order to avoid administration of DIPRIVAN Injection at rates higher than are clinically necessary. Generally, rates of 0.05 to 0.1 mg/kg/min should be achieved during maintenance in order to optimize recovery times. Intermittent Bolus: Increments of DIPRIVAN Injection 25 mg (2.5 mL) or 50 mg (5.0 mL) may be administered with introus oxide in patients undergoing general surgery. The incremental boluses should be administered when changes in vital signs indicate a response to surgical stimulation or light anesthesia. DIPRIVAN Injection has been used with a variety of agents commonly used in anesthesia, such as atropine, scopolamine, glycopyrrolate, diazepam, depolarizing and nondepolarizing muscle relaxants, and narcotic analgesics, as well as with inhalational and regional anesthetic agents. (See Drug Interactions.)

DOSAGE GUIDE

INDICATION	DOSAGE AND ADMINISTRATION		
Induction	Dosage should be individualized. Adults: Are likely to require 2.0 to 2.5 mg/kg (approximately 40 mg every 10 seconds until induction onset). Elderly, Debilitated, Hypovolemic, and/or ASA III or IV Patients: Are likely to require 1.0 to 1.5 mg/kg (approximately 20 mg every 10 seconds until induction onset).		
Maintenance Infusion	Variable rate infusion – titrated to the desired clinical effect. Adults: Generally, 0.1 to 0.2 mg/kg/min (6 to 12 mg/kg/h). Elderly, Debilitated, Hypovolemic, and/or ASA III or IV Patients: Generally, 0.05 to 0.1 mg/kg/min (3 to 6 mg/kg/h).		
Intermittent Bolus	Increments of 25 mg to 50 mg, as needed.		

Compatibility and Stability: DIPRIVAN Injection should not be mixed with other therapeutic agents prior to administration. Dilution Prior to Administration: When DIPRIVAN Injection is diluted prior to administration, it should only be diluted with 5% Dextrose injection, USP, and it should not be diluted to a concentration less than 2 mg/mL because it is an emulsion. In diluted form it has been shown to be more stable when in contact than 2 mg/mL because it is an emulsion. In diluted form it has been shown to be more stable when in contact with glass than with plastic (95% potency after 2 hours of running infusion in plastic.) Administration into a Running IV Catheter: Compatibility of DIPRIVAN injection with the coadministration of blood/serum/plasma has not been established. (See WARNINGS.) DIPRIVAN injection has been shown to be compatible with the following intravenous fluids when administred into a running IV catheter. 5% Dextrose injection. USP; Lactated Ringers and 5% Dextrose Injection, 5% Dextrose and 0.45% Sodium Chloride Injection, USP, 15% Dextrose and 0.25% Sodium Chloride Injection, USP, 5% Dextrose and 0.25% Sodium Chloride products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not use if there is evidence of separation of the phases of the emulsion. Strot aspectic techniques must always be maintained during handling as DIPRIVAN injection is a single-use parenteral product and contains no antimicrobial preservatives. The vehicle is capable of supporting rapid growth of microorganisms. DIPRIVAN injection should be prepared for use just prior to initiation of each individual anesthetic procedure. DIPRIVAN injection should be drawn into sterile syringes immediately after ampules or vials are opened. When using vials with volumetric infusion devices insert sterile vent spike through rubber stopper and immediately connect! Vi lie. Administration should of hours after procedure. DIPRIVAN Injection should be drawn into sterile syringes immediately after ampules or vials are opened. When using vials with volumetric infusion devices insert sterile vent spike through rubber stopper and immediately connect IV line. Administration should commence promptly and be completed within 6 hours after the ampules or vials have been opened. DIPRIVAN Injection should be prepared for single patient use only, and any unused options of DIPRIVAN Injection, reservoirs. It lines, or solutions containing DIPRIVAN Injection must be discarded at the end of the surgical procedure. Failure to follow aseptic handling procedures may result in microbial contamination causing fever and/or other adverse consequences which could lead to life-threatening illness. Aseptic Techinque* for Handling DIPRIVAN Injection Ampules.* Wear clean garments. *Wash hands and fingernails using an antimicrobial handwash. *When appropriate, wear sterile gloves, mask, and hair cover. Disinfect neck surface of ampule using 70% isopropyl alcohol. Swah neck of ampule by wiping in one direction and let dry. *Protect fingers and hands by using sterile gauze when opening the ampule. *Unitary DIPRIVAN Injection and a sterile syringe. *Immediately replace needle cap and discard ampule. *Label syringe with appropriate information. including date, time, and patient name. *Administer promptly. *Discard any unused DIPRIVAN Injection and reservoirs. IV lines, or solutions containing DIPRIVAN Injection and reservoirs. IV lines, or solutions containing DIPRIVAN Injection and reservoirs. IV lines, or solutions containing DIPRIVAN Injection and reservoirs in the end of the surgical procedure or within 6 hours —whichever occurs sooner. *Aseptic Technique* for Handling DIPRIVAN Injection and reservoirs in the end of the surgical procedure or within 6 hours —whichever occurs sooner. *Aseptic Technique* for Handling DIPRIVAN Injection and reservoirs in the end of the surgical procedure or within 6 hours — whichever occurs sooner. *Septic algorithmic



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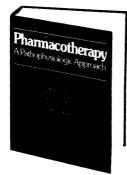
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Consider the Critical Parameters in Selecting a Neuromuscular Blocking Agent

	Norcuron® (vecuronium bromide) for injection
HEMODYNAMICS	Hemodynamic stability with no statistically significant variations in blood pressure, cardiac output, or systemic vascular resistance. 1,2
HISTAMINE	Clinical evidence indicates that reactions commonly associated with histamine release are unlikely to occur at doses up to 0.28 mg/kg. ¹⁻⁴
DURATION OF ACTION (0.08–0.1 mg/kg)	25–30 minutes (under balanced anesthesia).
DOSING FLEXIBILITY	Offers superior flexibility in long procedures: continuous infusion or high initial bolus dose. 5 "one can preselect a dose of vecuronium to produce either a short, medium, or long-acting degree of neuromuscular blockade without cardiovascular side effects." 6
STORAGE	Room temperature. No refrigeration required.
SHELF LIFE	2 years in lyophilized form.

Norcuron (vecuronium bromide) for injection

The Logical Choice for Neuromuscular Blockade

See following page for brief summary of prescribing information.



Norcuron[.] (vecuronium bromide) for injection

Before areacribing, piease consult complete aroduct information, a summary of which follows:

THIS DRING SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

CONTRAINDICATIONS: Noncuron® is contraindicated in patients known to bave a hypersensitivity to it.

WARNWIGS: NORCURON® SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILLAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT
MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION,
ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AMAILABLE. THE CLINICIAN
MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION, in patients were involved in lawer mysatherial graves or the
mysatheria (Eason-Lambert) syndrome, small doses or Norcestor® may have profound effects. In such patients, a peripieral
nerve stimulation and use of a small test dose may be of value in monitoring the response to administration of mescle

relocates.

PRECAUTIONS: General: Limited data on histamine assay and available clinical experience indicate that hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycerdia, and other reactions commonly associated with histarrine release are unfolely to occur.

Recal Faffunit: Norcuron® is well tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockade may occur; therefore, if anephric patients cannot be prepared for non-electhe surgery, a lower initial dose of horcuron® should be considered.

Attend Chresiation Time: Conditions associated with stower circulation time in cardiovascular disease, old age, edematous states resulting in increased volume of distribution may contribute to a delay in onset time, therefore desage should not be increased.

Increased.

Hapatita Diseases: Limited experience in patients with cirrbosis or choiestasis has revealed preferred except yime in keeping with the role the fiver plays in Noncurron* metabolism and excretion. Data currently evailable do not permit dosage recommendations in patients with impaired liver function.

Loag-term Use in LC.U. If the Intensive care unt, in rare cases, long-term use of neuromisscular blocking drugs to facilitate mechanical ventilation may be associated with protonged paralysis and/or skeletal muscle weakness that may be first noted during attempts to wear such patients from the ventilation. Typically, such patients recorde orther drugs such as broad spectrum arbitrotics, narcodics and/or steroids and may have electrolyle imbatance and diseases which lead to electrolyle imbatance, hypoxic episodes of varying duration, acid-base imbatance and estimate debilitation, any of which may enhance the actions of a neuromiscular blocking agent. Additionally, patients immobilized for excended periods frequently develop symptoms consistent with disease muscle stroptly. Therefore when there is a need for long-term mechanical ventilation, the benefits-to-risk ratio of neuromiscular blockade must be considered. Continuous institution or intermittent bolas dosing to support mechanical ventilation has not been studied sufficiently to support disease recommendations.

LNDER THE ABOVE CONDITIONS, APPROPRIME MONITIONING, SUCH AS USE OF A PENIPHERAL NERVE STIM-LUTUR, TO ASSESS THE DEGREE OF NEUROMASCULAR BLOCKADE, MAY PRECUDE INADVERTENT EXCESS DOSING. Severe Obesity or Neuromissasium sequiring special care before, during and after the use of neuromissatur disease may pose atively and/or ventilation problems requiring special care before, during and after the use of neuromissatur disease.

Severe Descriptor Naturalizatales Dissession Patients with severe obesity or neuronizatal refeases may pose arway and/or verificatory problems requiring special care before, dorting and after the use of neuronizatal refeases may pose arway and/or verificatory problems requiring special care before, dorting and after the use of neuronizatal blocking agents such as Norcarons.

It all patients the provide the second selected manufacture of the provided provided the second provided in susceptible animatis (swine) to establish whether or not Norcarons is capable of triggering malignant hyperthermia.

C. Ill. S.: Norcarons is an one loose affect on consciousness, the pain investod or construction and instruction of second provided in the second provided provided in the second provided provided in the second provided provided provided in the second provided prov

nitrous code, or dropenidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

Protinged parelysts and/or skeletal imuscle westross have been reported after long-term use to support mechanical ventilation in the Intensive care unit. (see PRECATIONS).

Bronchespasm, floshing, redness, hypotension and tachycardia have been reported in very rare instances.

OVERDOSAGE. The possibility of latrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation.

Excessive dosse of Norcaron® produce enhanced pharmacological effects. Restitual neuromascular blockage beyond the time period needed may occur with Norcaron® as with other neuromascular blockers. This may be manifested by skeletal muscle weatness, decreased respiratory reserve, low tidal volume, or panea. A peripheral mere stimulation may be used to assess the degree of residual neuromascular blockade from other causes of decreased respiratory reserve.

Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcottics, thicharchiturates and other control nervous system depressants. Under such cardiocal engineering treatment is maintenance of a patient almost an analysis of mechanical ventilation until complete recovery of normal respiration is assured. Regonol® (pridostignine bromide) injection, neostignine, or elicophonism. In this presence of extreme distillation of which height. Fallure of prompt reversal within 30 minutes) may conjunction with attropine or glycopytrolate will usually antagonize the sicetati muscle releasant action of Norcaron®, Satisfactory reversal can be judged by adequatory of sidetatal muscle lone and by adequatory of respiration. A peripheral nerve stimulation may also be used to monitor restoration of which height. Fallure of prompt reversal within 30 minutes) may conjunction with a tropine of their own. Interpretate see only. This drug should be adm

anesthatics and by prior use of succinytcholine (see PRECAUTIONS-0) reg interactions). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. To obtain maximum clinical benefits of Norcaron® and in minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial does of Norcaron® is 0.08 to 0.10 mg/tg (1.4 to 1.75 times the ED₀₀) given as an intravenous bolts injection. This does can be expected to produce good or excellent non-emergency intuition conditions to 2.5 to 3 minutes after injection, under behavior behavior approximately 25-30 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection. Under behavior approximately 45-65 minutes after injection. In the presence of potent inhabition anesthesis are the neuron social blocking effect of Norcaron® is enhanced. If Norcaron® is first administrated more than 5 minutes after the start of inhabition agent or when steady state has been achieved, like Initial Norcaron® to 800 to 0.056 mg/tg.

Prior administration of succinyteholine may enhance the neuron social blocking effect and duration of action of Norcaron®, it intuitions is performed using succinyteholine, a reduction of inhibit does of Norcaron® to 0.04-0.06 mg/tg with inhabition anesthesis and 0.05-0.06 mg/tg with inhabition and prior and

necessary to reduce the cate of infusion.

Spontaneous recovery and reversal of necessary to reduce the cate of infusion blockade following discontinuation of Norcuron® Infusion may be expected to proceed at natice comparable to that following a single boths dose.

Infusion solutions of Norcuron® can be prepared by mixing Norcuron® with an appropriate infusion solution such as 5% glucose in water, 0.9% NaCl, 5% glucose in satine, or Lactated Ringers. Unused portions of infusion solutions should be infusion rates of Norcuron® can be individualized for each patient using the following table:

Drug Delivery Rate	ħ.	ufusion Delivery Rada
(μg/kg/min)	0.1 mg/mL*	(mL/kg/min) 0.2 mg/mL†
0.7	0.007	0.0035
0.8	0.008	0.0040
0.9	0.009	0.0045
1.0	0.010	0.0050
1.1	0.011	0.0055
1.2	0.012	0.0060
1.3	0.013	0.0065

10 mg of Norcuron in 100 mL solution †20 mg of Norcuron* in 100 mL solution g of Norcuron® in 100 mi., solution

The following table is a guideline for mi./min delivery for a solution of 0.1 mg/mi. (10 mg in 100 ml.) with an infusion pump. NORCHBON® INFLISION RATE --- mi ANIN

Amount of Drug		Pat	ent Weight	- ko			
μ α/κα/πύ π	40	50	60	70 T	80	90	100
0.7	0.28	0.35	0.42	0.49	0.56	0.63	0.70
0.8	0.32	0.40	0.48	0.56	0.64	0.72	0.80
0.9	0.38	0.45	0.54	0.63	0.72	0.81	0.90
1.0	0.40	0.50	0.60	0.70	0.80	0.90	1.00
1.1	0.44	0.55	0.66	0.77	0.88	0.99	1.10
12	0.48	0.60	0.72	0.84	0.96	1.08	1.20
13	0.52	0.65	0.7E	0.91	1 04	1 17	1 30

NOTE: If a concentration of 0.2 mg/ml, is used (20 mg in 100 ml.), the rate should be decreased by one-half.

HOTE: If a concentration of 0.2 mg/ml, is used (20 mg in 100 mil.), the rate should be decreased by one-balf.

Dasage is Childran. Older children (10 to 17 years of age) have approximately the same design engulnments (mg/mg) as studies and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial does and may also require supplementation stightly more often than adults. Infants under one year of age bad older than 7 weeks are moderately more sensible to Norcuron* on a mg/mg basis than adults and thise about 112 times also long to recover. See also subsection of PRECAUTIONS titled Pediatric Use. Information presently available does not permit recommendation on usage in neonates (see PRECAUTIONS). There are insertificient data concerning continuous infusion of vecuroritism in children flarefore, no doesing recommendation can be made.

COMPRITIBILITY: Norcuron* is compatible in solution with:

0.94 NaCL solution

5% glucose in water

Serille water for injection

Use within 24 hours of mixing with the above solutions.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

STURABEL 15-30°C (99-96°F). Protect from light.

AFTER REDINSTITUTIONE:

When reconstituted with supplied bacterlossatic water for injection: CONTAINS BENZYL ALCOHOL, WHICH IS NOT AUTONOME.

- r con recurrent to travel:

 When reconstituted with supplied bacteriostatic water for trijection; CONTAINS BENZYL ALCOHOL, WHICH IS NOT

 INTENDED FOR USE IN NEWBORNS, Use within 5 days. May be stored at room temperature or refrigerated.

 When reconstituted with sterile water for injection or other compatible I.V. solutions; Refrigerate vial. Use within 24 hours, Single use only. Discard unused portion.

 REV. 3. References:
- 1. Norcuron® (vecuronium bromide) for injection package insert.
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MARCH 1991

Mock Orals Help Dr. Smith

Home-study, lectures, and practice oral exams - limited to 90 participants

The Osler Institute Anesthesiology Boards Tutorial

July 6-11, 1991 — Chicago August 9-12, 1991 — Atlanta August 15-19, 1991 — Chicago August 23-26, 1991 — Los Angeles September 30-October 5 — Tampa

Dear Fellow Physician:

Dr. Smith (not his real name) had failed his oral boards several times. His group was satisfied with his work but his job depended on becoming board certified. He was eligible to take the exam only one more time. A friend advised him to take our Osler Institute's Anesthesiology Board Review

Home Study Questions

Before the course, we sent him several hundred pages of multiple choice questions with answers as well as keywords with explanations. These were given to us by past participants. Now we also have a collection of mock-oral-exam stem cases and related questions to send you.

Free Sample Offer

We offer to send you a gift without obligation: a free sample of our multiple choice questions or our mock oral cases. We would like to share these with you whether or not you take our course. Please request on course registration form.

Complete Syll abus

We can also send you a copy of a previous course syllabus. Our price to you is \$60 (about our production cost). The supply is limited. Those registering for the six day lecture course will receive several hundred pages of current lecture notes and all home study materials at no extra charge.

Great Lectures

At the course, Dr. Smith enjoyed six days of outstanding lectures by some of the best-known teachers in anesthesiology — as well as by several outstanding junior faculty who had been asked back because of their excellent participant evaluation scores. Also several new faculty had been recommended for their speaking ability.

Some of the lectures were of little use to Dr. Smith — he is regarded as an expert in his

field; he could have given several of the lectures himself. Knowledge was not his problem; his problem was presenting his knowledge in the oral exam. He skipped several lectures to attend:

Mock Oral Exams

The first day of the course, a recently retired board examiner explained the philosophy, process, and scoring of the real oral exam. Each evening as well as concurrent with most lectures there were mock oral exams for Dr. Smith. These are group sessions with one participant taking the hot seat for about 25 minutes while others watch. Each participant is entitled to a turn in the hot seat as well as unlimited observation of others.

When Dr. Smith took the hot seat his heart quickened, his palms sweated, and his hands shook. The faculty presented a stem question, paused a minute, then asked the first question. Dr. Smith opened his mouth, but his tongue was thick and dry. He stammered and stuttered — failed to form even a sentence — just like when he failed the real oral exam. But this time was different; the faculty coached and encouraged him. His panic passed and his performance improved.

Extra Mock Orals

The course budget could not support enough faculty for an unlimited number of mock orals for every participant. In our previous course, assertive attendees had taken the hot seat repeatedly before others had a chance. In response, we mark participant name tags for the first mock oral. We also hire additional faculty time and sell \$70 tickets for extra turns in the hot seat.

Dr. Smith became more comfortable in the hot seat. He continued to improve.

Private and Dual Orals

Dr. Lee, however, was too shy to take the hot seat in front of anyone else. We now have a thirty dollar surcharge for private sessions. Also, Dr. Jones wanted two examiners, just like the real exam. Such sessions take twice the faculty time, so we must charge \$140 per session.

Video Mock Orals

At our June course, we had a portable TV studio to make educational tapes with some of the faculty. Video taping mock orals was so popular that we now offer a video tape of your practice exam for an extra ten dollars per session.

Extra Mock Oral Days

Lectures end on Saturday and the real oral exams are the next Monday through Friday. What do you do in the meantime? Sunday through Tuesday of oral exam week are optional extra days of mock oral exams. For \$140 per day, attendees receive one 25 minute hot seat session and observation of other sessions for nine hours.

Your Individual Needs

The quality of our courses gave us growth. Growth helped us improve to meet your individual needs. At the course, you may choose every hour between a lecture or observation of one-on-one mock oral exams.

Passing Your Boards

Will our course help you pass your boards? Dr. Smith passed his oral exam the week after our course. A candidate calling to register for our course told us:

"Five of my partners took your course; they all passed their oral boards; and they all recommended your course."

One of our faculty reported:

"All of my residents who took the course passed their boards."

We can't guarantee that you will pass. We can't say that taking our course will make the difference between passing or failing. All we can say is that a lot of our participants tell us that the course was helpful. See registration form to request a free sample.

We look forward to meeting you at our course and helping you to pass your board exams.

Cordially,

Joseph H. Selliken, Jr., M.D.

P.S. To reserve your place call today

(800) 356-7537

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The Netherlands JOURNAL OF MEDICINE

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FOR THE INTERNAL
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Aims and Scope:

The Netherlands Journal of Medicine publishes original articles and reviews in all relevant fields of internal medicine. In addition to clinically oriented papers, manuscripts containing experimental data, including both laboratory and animal studies, are considered for publication. The "Brief Reports" section allows for the publication of concise reports on original work, while Case Reports, which are relevant for understanding the pathophysiology or clinical presentation of internal diseases may also be accepted under this heading. Furthermore, book reviews and a correspondence section are regular items in the Journal.

An International Advisory Board has been established, consisting of outstanding scientists, all distinguished investigators in various fields of internal medicine.

Since 1987 the Journal has been published in two editions: a monthly edition for the Netherlands audience and a bimonthly edition for the international audience.

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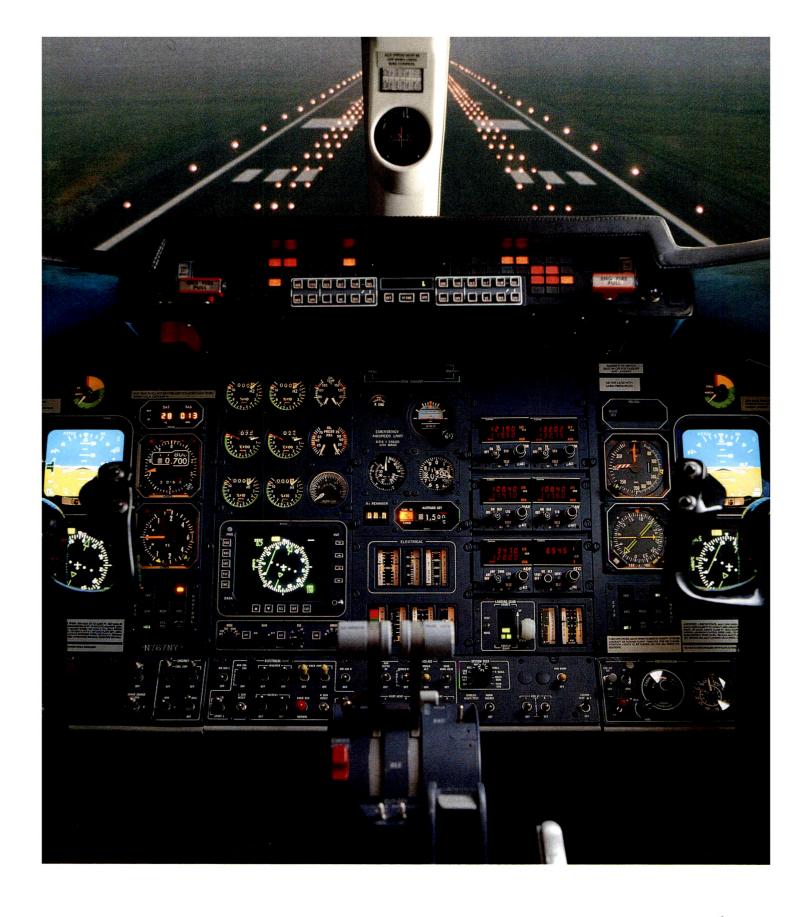
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Precise Control



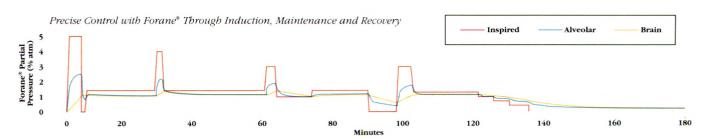
Precise Hands

Before Surgical Incision

Overpressuring* with Forane® rapidly achieves the desired anesthetic tension in the brain, giving you confidence that your patient is ready for surgery.

During Maintenance

Alveolar concentrations of Forane® are easily monitored and adjusted to accommodate your patient's changing anesthetic requirements.



Overpressuring requires the use of an inspired concentration that can cause cardiovascular depression if administered for a sufficient period of time. Thus, the anesthetist must closely monitor blood pressure and heart rate during the period overpressure is used.

Graph generated from a computer simulation, depicting the relationship between inspired, alveolar and brain partial pressures throughout a surgical procedure. During maintenance, brief periods of overpressure are used to accommodate the patient's changing anesthetic requirements during times of increased surgical stimulation.

 $^{^\}dagger$ GUS Computer Simulation. GUS is a registered trademark of Quincy Street Corporation, Phoenix, AZ.



n Control

Upon RecoveryPrecise control of anesthetic depth and rapid elimination of Forane® through the lungs facilitate an uneventful postanesthetic course for your patient.

Please refer to Prescribing Information on the following page.



Precise Hands-On Control





Precise Hands-On Control

CAUTION: Federal Law Prohibits Dispensing without Prescription

DESCRIPTION

ne. USP) a nonflammable liquid administered by vaporizing, is a general inhalation anesthetic drug -trifluoroethyl difluoromethyl ether, and its structural formula is. FORANE (isoflurane, I It is 1-chloro-2,2,2-trif

ne physical constants are.		
Molecular weight		184.5
Boiling point at 760 mm Hg		48.5 °C (uncorr.)
Refractive index n		1 2990-1 3005
Specific gravity 25 °/25 °C		1.496
Vapor pressure in mm Hg**	20 °C	238
	25 °C	295
	30 °C	367
	35 °C	450
quation for vapor pressure calculation		
log P - A · B		

Partition coefficients at 37 °C	
Water/gas	0.61
Blood/gas	1 43
Oil/gas	90.8
Partition coefficients at 25 °C · rubber and plastic	
Conductive rubber/gas	62.0
Butyl rubber/gas	75.0
Polyvinyl chloride/gas	110.0
Polyethylene/gas	~2.0
Polyurethane/gas	~1.4
Polyolefin/gas	~1.1
Butyl acetate/gas	~2.5
Purity by gas chromatography	~ QQ Q S

Purity by gas chromatography Lower limit of flammability in oxygen or nitrous oxide at 9 joules/sec and 23 ° Lower limit of flammability in oxygen or nitrous oxide at 900 joules/sec and 23 °

Isoflurane is a clear, coloriess, stable liquid containing no additives or chemical stabilizers. Isoflurane has a mildly pungent, musty, ethereal odor. Samples stored in indirect sunlight in clear, coloriess glass for five years, as well as samples directly exposed for 30 hours to a 2 amp. 115 volt, 60 cycle long wave UV light were unchanged in composition as determined by gas chromatography. Isoflurane in one normal sodium methoxide methanol solution, a strong base, for over six months consumed essentially no alkali, indicative of strong base stability. Isoflurane does not attack aluminum, tin, brass, iron or copper.

CLINICAL PHARMACOLOGY

ation anesthetic. The MAC (minimum alveolar concentration) in man is as follows

Age	100% Oxygen	70% N ₂ O
26 ± 4	1.28	0.56
44 ± 7	1.15	0.50
64 ± 5	1.05	0.37

Induction of and recovery from isoflurane anesthesia are rapid. Isoflurane has a mild pungency which limits the rate of induction, although excessive salvation or tracheobronchial secretions do not appear to be stimulated. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia may be changed rapidly with soflurane is a profound respiratory depressant. RESPIRATION MUST BE MONITORED CLOSELY AND SUPPORTED WHEN NECESSARY As anesthetic does is increased, tidal volume decreases and respiratory rate is unchanged This depression is partially reversed by augical stimulation, even at deeper levels of anesthesia. Isoflurane evokes a sigh response reminiscent of that seen with deathly either and enflurane, although the frequency is less than with enflurane.

reminiscent of that seen with diethyl either and enflurane, although the frequency is less than with enflurane. Blood pressure decreases with induction of anethesa but returns toward normal with surgicial stimulation. Progressive increases in depth of anesthesia produce corresponding decreases in blood pressure. Nitrous oxide diminishes the inspiratory concentration of software required to reach a desired level of anesthesia and may reduce the arterial hypotension seen with isoflurane alone. Heart rhythm is remarkably stable. With controlled ventilation and normal PaCO₂ cordiac output is maintained despite increasing depth of anesthesia primarily through an increase in heart rate which compensates for a reduction in stroke volume. The hypercapnia which attends spontaneous ventilation during isoflurane anesthesia further increases heart rate and raises cardiac output above awake levels is follurane does not sensitize the myocardium to exogenously administered epinephrine in the dog Limited data indicate that subcutaneous injection of 0.25 mg of epinephrine (50 mL of 1.200,000 solution) does not produce an increase in ventricular arrhythmias in patients anesthetized with isoflurane.

in patients anesthetized with isolutiane Muscle relaxation is often the transparence of the transparence o

Isoflurance an produce cornorary vasodiation at the attential revel in selected animal models ^{1,2} the drug is probably also a coronary dilator in humans. Isoflurance, like some other coronary attential ratios, has been shown to divert blood from collateral dependent myocardium to normally perfused areas in an animal model [7 coronary steal]. Clinical studies to date evaluating myocardial ischemia, infarction and death as outcome parameters have not established that the coronary attentiolal dilation property of isoflurane is associated with coronary steal or myocardial ischemia in patients with coronary attentions.

Pharmacokinetics: Isoflurane undergoes minimal biotransformation in man. In the postanesthesia period, only 0.17% of the isoflurane taken up can be recovered as urinary metabolites.

INDICATIONS AND USAGE
FORANE (isoflurane, USP) may be used for induction and maintenance of general anesthesia. Adequate data have not been developed to establish its application in obstetrical anesthesia.

CONTRAINDICATIONS
Known sensitivity to FORANE (isoflurane, USP) or to other halogenated agents.

Known or suspected genetic susceptibility to malignant hyperthermia

WARNINGS

viets of an esthesia may be altered easily and rapidly, only vaporizers producing predictable concentrations should I. Hypotension and respiratory depression increase as anesthesia is deepened. ed blood loss comparable to that seen with halothane has been observed in patients undergoing abortions be used. Hypotens

FORANE (isoflurane, USP) markedly increases cerebral blood flow at deeper levels of anesthesia. There may be a transient rise in cerebral spinal fluid pressure which is fully reversible with hyperventilation.

PRECAUTIONS

FREGULIONS
General: As with any potent general anesthetic, FORANE (isoflurane, USP) should only be administered in an adequately equipped anesthetizing environment by those who are familiar with the pharmacology of the drug and qualified by training and experience to manage the anesthetized patient

Regardless of the anesthetics employed, maintenance of normal hemodynamics is important to the avoidance of myocardial ischemia in patients with coronary artery disease 4.5.6.7

Information to Patients: Isofurane, as well as other general anesthetics, may cause a slight decrease in intellectual function for 2 or 3 days following anesthesia. As with other anesthetics, small changes in moods and symptoms may persist for up to 6 days after administration.

Laboratory Tests: Transient increases in BSP retention, blood glucose and serum creatinine with decrease in BUN, serum cholesterol and alkaline phosphatase have been observed.

Drug Interactions: Isoflurane potentiates the muscle relaxant effect of all muscle relaxants, most notably nondepolarizing muscle relaxants and MAC (minimum alveolar concentration) is reduced by concomitant administration of N_2 O See CLINICAL PHARMACOLOGY

See CLINIOLI PTAKING CLICOT:

Carcinogenesis: Swiss ICR mice were given isoflurane to determine whether such exposure might induce neoplasia isoflurane was given at 1/2, 1/8 and 1/32 MAC for four in-utero exposures and for 24 exposures to the pups during the first nine weeks of life. The mice were killed at 15 months of age. The incidence of tumors in these mice was the same as in untreated control mice which were given the same background gases, but not the anesthetic

Pregnancy Category C: Isoflurane has been shown to have a possible an esthetic related fetoxic effect in given in doses 6 times the human dose. There are no adequate and well-controlled studies in pregnant womer should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk. Because many drugs are excreted in human milk. Because many drugs are excreted in human milk. Caution should be exercised when isoflurane is administered to a nursing woman.

Malignant Hyperthermia: In susceptible individuals, isoflurane anesthesia may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hypertherma. The syndrome includes nonspecific features such as muscle rigidity, tachycardia, tachyprae, cyanosis, arrhythmias, and unstable blood pressure (It should also be noted that many of these nonspecific signs may appear with light anesthesia, actual hypoxia, etc.) An increase in overall metabolism may be reflected in an elevated temperature (which may rise rapidly early or late in the case, but usually is not the first sign of augmented metabolism) and an increased usage of the CO₂ absorption system (hot canstel; PaO₂ and pH may decrease, and hyperkalemia and a base deficit may appear Theatment includes discontinuance of triggering agents (e.g., isoflurane), administration of intravenous dantrolene sodium and application of supportive therapy. Such therapy includes vigorous efforts to restore body temperature to normal, respiratory and circulatory support as indicated, and management of electrolyte-fluid-acid-base derangements (Consult prescribing information for dantrolene sodium intravenous for additional information on patient management.)

Renal failure may appear later, and urine flow should be sustained if possible.

ADVERSE REACTIONS

Adverse reactions encountered in the administration of FORANE (isoflurane, USP) are in general dose dependent ex-tensions of pharmacophysiologic effects and include respiratory depression, hypotension and arrhythmias

Shivering, nausea, vomiting and ileus have been observed in the postoperative period

As with all other general anesthetics, transient elevations in white blood count have been observed even in the absence of surgical stress.

See PRECAUTIONS for information regarding malignant hyperthermia

dosage, or what may appear to be overdosage, the following action should be taken

Stop drug administration, establish a clear airway and initiate assisted or controlled ventilation with pure oxygen

DOSAGE AND ADMINISTRATION

Premedication: Premedication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by FORANE (isoflurane, USP) and the heart rate tends to be increased. The use of anticholinering critique is a matter of choice.

Inspired Concentration: The concentration of isoflurane being delivered from a vaporizer during anesthesia should be known. This may be accomplished by using:

- a) vaporizers calibrated specifically for isoflurane
- vaporizers from which delivered flows can be calculated, such as vaporizers delivering a saturated vapor which is then diluted. The delivered concentration from such a vaporizer may be calculated using the formula

Isoflurane contains no stabilizer. Nothing in the agent alters calibration or operation of these vaporizers

Induction: Induction with isoflurane in oxygen or in combination or operation of these vaporizers dudiction: Induction with isoflurane in oxygen or in combination with oxygen-nitrous oxide mixtures may produce coughing, breath holding, or laryngospasm. These difficulties may be avoided by the use of a hypnotic dose of an ultrashort-acting barbiturate. Inspired concentrations of 1.5 to 3.0% isoflurane usually produce surgical anesthesia in 7 to 10 minutes.

Maintenance: Surgical levels of anesthesia may be sustained with a 1 0 to 2 5 % concentration when nitrous oxid ed concomitantly. An additional 0 5 to 1 0 % may be required when isoflurane is given using oxygen alone. If added relist required, supplemental doses of muscle relaxants may be used.

The level of blood pressure during maintenance is an inverse function of isoflurane concentration in the absence of other complicating problems. Excessive decreases may be due to depth of an esthesia and in such instances may be corrected by lightening an esthesia.

HOW SUPPLIED
FORANE (Isoflurane, USP), NDC 10019-360-40, is packaged in 100 mL amber-colored bottles

Storage: Store at room temperature $15^{\circ} \cdot 30^{\circ}\text{C} (59^{\circ} \cdot 86^{\circ}\text{F})$ Isoflurane contains no additives and has been demonstrated to be stable at room temperature for periods in excess of five years

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Comparison of Hypobaric, Hyperbaric, and Isobaric Solutions of Bupivacaine During Continuous Spinal Anesthesia

Elisabeth F. Van Gessel, MD, Alain Forster, MD, Alexandre Schweizer, MD, and Zdravko Gamulin, MD

VAN GESSEL EF, FORSTER A, SCHWEIZER A, GAMULIN Z. Comparison of hypobaric, hyperbaric, and isobaric solutions of bupivacaine during continuous spinal anesthesia. Anesth Analg 1991;72:779–84.

This study was designed to compare the anesthetic properties of hypobaric bupivacaine with those of isobaric and hyperbaric solutions when administered in the supine position in an elderly population undergoing hip surgery using continuous spinal anesthesia. Plain bupivacaine (0.5%) was mixed with equal volumes of 10% dextrose (hyperbaric), 0.9% NaCl (isobaric), or distilled water (hypobaric) to obtain 0.25% solutions. In a double-blind fashion, all patients received 3 mL (7.5 mg) of their particular solution injected through the spinal catheter in the horizontal supine position. The sensory level obtained in the hyperbaric group (median, T4; range, T3-L3) was significantly higher than in both the isobaric (median, T11; range, T6-L1) and hypobaric (median, L1; range, T4-L3) groups. A motor blockade of grade 2 or 3 was obtained in 14 of 15 and 12 of 15 patients in, respectively, the hyperbaric and isobaric groups, but only in 8 of 15 patients in the hypobaric group. After the initial injection of 3 mL (7.5 mg), a sensory level of T19 and a motor blockade of grade 2 or 3 was obtained in 14 of 15, 5 of 15, and 3 of 15 patients in the hyperbaric, isobaric, and hypobaric groups, respectively. All remaining patients received 1 or 2 additional milliliters (2.5-5 mg) and achieved these required anesthetic conditions, except for one patient in the hyperbaric group and eight patients in the hypobaric group in whom anesthesia was achieved with hyperbaric tetracaine. The decrease in mean arterial pressure was significantly more severe in the hyperbaric (30%) than in either the isobaric (18%) or hypobaric (14%) groups. The authors conclude that isobaric bupivacaine used during continuous spinal anesthesia in the supine horizontal position produces a suitable and more "controllable" anesthesia for surgical treatment of fractured hips in geriatric patients. Under similar conditions, hyperbaric bupioacaine produces major hemodynamic consequences with high cephalad spread and hypobaric bupivacaine has too high an incidence of failure.

Key Words: ANESTHETIC TECHNIQUES, SPINAL. ANESTHESIA, ORTHOPEDIC.

Bupivacaine is increasingly used for spinal anesthesia and is found to be comparable in potency and in duration to tetracaine (1–4). Previous studies (5–7) have compared the clinical effects of hyperbaric and isobaric solutions of bupivacaine using single-injection spinal anesthesia with patients in the supine position. The conclusions were that the cephalad spread produced by the hyperbaric solutions was generally significantly greater than with the isobaric solutions. However, the predictability of the extent of the sensory blockade seemed poor for both solutions (8–11). Likewise, hypotension was also greater with

the hyperbaric solutions because of the more extensive sensory and sympathetic denervation (5,6).

Although a hypobaric solution of bupivacaine has recently been shown to be reliable for hip surgery in the lateral decubitus position in elderly patients (12), to our knowledge the same solution has never been tested with patients supine. This study was designed to compare the anesthetic behavior and hemodynamic consequences produced by a hypobaric solution of bupivacaine with those produced by isobaric and hyperbaric solutions when administered in the supine position in an elderly population undergoing hip surgery using continuous spinal anesthesia (CSA). This technique allows the administration of small incremental doses of local anesthetics (LAs) and thus provides a more "controllable" sensory and sympathetic level, reduces the total dosage of LAs administered, and is associated with a low incidence

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of failure (1.7%) (13). Furthermore, as a clinical investigational tool, CSA, in our opinion, permits a more precise comparison to be made of LAs than singleinjection spinal anesthesia of whatever concentration, volume, or baricity.

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Methods

After institutional approval, informed consent was obtained from 45 patients, all older than 75 yr, scheduled for elective hip surgery under CSA. These patients were randomly divided into three groups according to spinal anesthetic received: hyperbaric, isobaric, and hypobaric bupivacaine. Disoriented patients were excluded, in addition to patients with the usual contraindications to spinal anesthesia.

Preoperative medication consisted of 0.5 mg/kg intramuscular meperidine and 0.25 mg/kg promethazine 1 h before the patient's arrival in the operating room. Heart rate and arterial pressure were then measured with a noninvasive automatic blood pressure device, and the electrocardiogram was continuously monitored. More invasive monitoring (i.e., central venous pressure, arterial line, or indwelling urinary catheter) was used only if required by the patient's clinical condition.

Preanesthetic hydration consisted of 10 mL/kg of a crystalloid solution infused over 20–30 min, followed immediately after the injection of the local anesthetic by another 5 mL/kg given over 30 min. Thereafter, fluids were administered on the basis of changes in arterial pressure or, when monitored, on that of changes in central venous pressure and urinary output. Blood loss was replaced with a crystalloid solution on a 3:1 basis until estimated or measured hematocrit reached 35%; further losses were replaced by blood.

The lumbar puncture was performed using the midline approach at the L2-3 (or L3-4) interspace with an 18-gauge Tuohy needle; a 20-gauge spinal catheter was then introduced 3-4 cm in a cephalad direction and the patient turned back to the horizontal supine position for the rest of the study. In all patients 3 mL of either 0.25% bupivacaine solution (i.e., hyperbaric, isobaric, or hypobaric) was injected in a double-blind manner at a rate of 1 mL/min. The three solutions were prepared as follows: 5 mL of plain 0.5% bupivacaine was mixed with equal volumes of either 10% dextrose (hyperbaric at 2.5 mg/mL or 0.25%), 0.9% NaCl (isobaric at 2.5 mg/mL or 0.25%), or distilled water (hypobaric at 2.5 mg/mL or 0.25%).

The following variables were measured every 5 min during the first 30 min after the intrathecal injection: (a)

progression and upper level of sensory blockade, evaluated by pinprick; (b) quality of motor blockade according to the Bromage scale, ranging from 0 indicating no motor blockade to 3 indicating complete motor blockade (14); and (c) progression and upper level of loss of temperature discrimination (sympathetic blockade, determined indirectly by use of the ether swabs).

Thirty minutes after the initial injection of 3 mL (7.5 mg) of either solution, a sensory level lower than T10 or a motor blockade less than grade 2 prompted the reinjection of 1 mL (2.5 mg) of the same anesthetic solution, followed 10 min later by an additional milliliter (2.5 mg) if necessary. If 10 min after the second reinjection, the desired level of analgesia or degree of motor blockade had not been obtained, the anesthesia was considered a failure and 0.5% hyperbaric tetracaine was injected.

The following variables were measured: (a) duration of sensory blockade, defined by the reappearance of pain at the operative site requiring a reinjection of 1 mL of the same anesthetic solution used; (b) incidence and amount of vasopressors and/or anticholinergics used; (c) total amounts of crystalloids and blood infused; (d) arterial pressure and heart rate, measured before the anesthetic injection and every 2.5 min thereafter until the end of surgery; and (e) central venous pressure and urinary output, when possible every 30 min.

The frequency of clinically important hypotension, defined as a decrease in systolic arterial pressure of 30% or more below preoperative baseline levels, as well as frequency of decreases in heart rate of more than 20%, were recorded. These hemodynamic changes were treated with 5 mg intravenous ephedrine and 0.5 mg intravenous atropine sulfate, respectively.

All patients were clinically assessed during their stay in the hospital until discharge. Incidence of postspinal headache as well as mean duration of hospitalization and mortality was recorded.

All results are expressed as mean \pm sp, or as median (range) for ordinal data. Analysis of variance, the Kruskall-Wallis test, the Mann-Whitney U test, and the χ^2 or Fisher's exact test were used as required.

Results

There were 15 patients in each group. As summarized in Table 1, demographic and preanesthetic hemodynamic data were comparable in the three groups. Surgery lasted 134 ± 23 min in the hyperbaric group, 146 ± 53 min in the isobaric group, and $124 \pm$

Table 1. Patient Characteristics and Preanesthetic Hemodynamic Variables

	Hyperbaric $(n = 15)$	Isobaric (n = 15)	Hypobaric (n = 15)
Age (yr)	84 ± 6	86 ± 4	85 ± 6
Weight (kg)	60 ± 14	63 ± 14	62 ± 16
Height (cm)	161 ± 7	163 ± 7	160 ± 10
ASA status (II/III/IV)	1/13/1	0/14/1	0/13/2
MAP (mm Hg)	104 ± 16	100 ± 11	105 ± 20
HR (beats/min)	80 ± 13	75 ± 12	74 ± 10

MAP, mean arterial pressure; HR, heart rate. All values, except for ASA status, are expressed as mean ± sp.

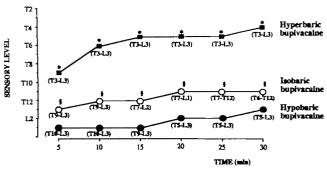


Figure 1. Comparison between the three groups of the spread of sensory level in the first 30 min after initial administration of 3 mL (7.5 mg) of bupivacaine (median; range in parentheses). *Significantly different from the two other groups (P < 0.01). §P <0.05 for isobaric versus hypobaric.

46 min in the hypobaric group, with no significant differences between groups.

Sensory Blockade

Cephalad spread of sensory blockade, assessed by pinprick (Figure 1), was significantly higher at all times with the hyperbaric solution than with the two other solutions (P < 0.01). A significant difference was also observed between the isobaric and hypobaric solutions (P < 0.05). The maximum sensory and sympathetic levels (Table 2) were all significantly different between the three groups (P < 0.01 and 0.05). However the mean time to reach these levels was significantly different only when comparing the hyperbaric with the hypobaric group (P < 0.01).

Motor Blockade

Table 2 also shows the number of patients with a motor blockade of grade 2 or 3. An adequate motor blockade as defined previously was observed in a

Table 2. Anesthetic Characteristics After Initial 3-mL (7.5 mg) Injection

	Hyperbaric $(n = 15)$	Isobaric (n = 15)	Hypobaric $(n = 15)$
Maximum sensory level [median (range)]	T4 (T3-L3)*	T11 (T6-12) ^b	L1 (T5-L3)
obtained after (min) (mean \pm sp)	$17 \pm 8^{\circ}$	22 ± 8	26 ± 5
Maximum sympathetic level [median (range)]	T4 (T2-L3) ^a	T9 (T5-11) ^b	T11 (T4-L3)
obtained after (min) (mean ± sp)	19 ± 7°	22 ± 8	26 ± 5
No. of patients with grade 2 or 3 motor blockade	14 ^d	12	8

Significantly different from the two other groups (P < 0.01). ^bSignificantly different between isobaric and hypobaric groups (P <

Significantly different between hyperbaric and hypobaric groups (P <

0.01). d Significantly different between hyperbaric and hypobaric groups (P < 1

comparable number of patients in both hyperbaric and isobaric groups. However only 8 of 15 patients in the hypobaric group achieved a grade 2 or 3 motor blockade, and this was significantly lower than in the hyperbaric group (P = 0.05). For all these patients, the mean time to onset of this blockade was 12 \pm 9 min in the hyperbaric group (n = 14), 19 ± 8 min in the isobaric group (n = 12), and 19 ± 9 min in the hypobaric group (n = 8); there were no significant differences between groups.

Hemodynamic Changes

The hemodynamic effects of the initial 3-mL injection of anesthetic solution, as well as the number of patients given ephedrine and its mean total dosage, are reported in Table 3. Significantly greater decreases in mean arterial pressure (MAP) (P < 0.01)and heart rate (P < 0.05) were observed in the hyperbaric group with consequently also a greater number of patients receiving ephedrine (P < 0.05).

Quality of Anesthesia

Table 4 presents the incidence of adequate anesthesia and incidence of anesthetic failure. Thirty minutes after the initial 3-mL injection of bupivacaine, 14 of 15 patients in the hyperbaric group had adequate anesthetic conditions as defined previously, whereas anesthesia was satisfactory in significantly fewer patients of both the isobaric (5 of 15, P < 0.01) and the

Table 3. Hemodynamic Changes Observed During the First 30 min After Initial 3-mL (7.5 mg) Injection

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	Hyperbaric $(n = 15)$	Isobaric $(n = 15)$	Hypobaric $(n = 15)$
Maximum changes from preanesthetic baseline values in			
MAP (%)	$-30 \pm 16^{\circ}$	-18 ± 13	-14 ± 9
HR (%)	-17 ± 8^{b}	-11 ± 4	-12 ± 5
Time to reach maximal changes in			
MAP (min)	14 ± 7	17 ± 9	16 ± 9
HR (min)	14 ± 9	18 ± 9	16 ± 10
No. of patients receiving ephedrine	94	1	1
Mean dosage ephedrine (mg)	12 ± 5	5	5

MAP, mean arterial pressure; HR, heart rate. Values for MAP and HR are given as mean \pm sp. *Significantly different from the two other groups (P < 0.01).

Table 4. Incidence of Adequate Anesthesia After Initial Injection, After One or Two Reinjections, and Incidence of Anesthetic Failure (n = 15 for each group)

	Ade	***************************************		
	Initial injection (7.5 mg)	One reinjection (7.5 + 2.5 mg)	Two reinjections (7.5 + 2.5 + 2.5 mg)	Anesthetic failure
Hyperbaric	14"		_	1
Isobaric	5	6	4	*********
Hypobaric	3	3	1	8*

"Significantly different from the two other groups (P < 0.01).

hypobaric (3 of 15, P < 0.01) groups. One anesthetic failure was observed in the hyperbaric group after the patient had received a total dose of 12.5 mg of bupivacaine. The remaining 10 patients in the isobaric group received one or two reinjections of the same solution, and all consequently achieved a sensory level of T10 and a motor blockade of grade 2 or 3. Of the remaining 12 patients in the hypobaric group, four achieved the desired levels of sensory and motor blockade with one or two reinjections; the eight remaining patients all required hyperbaric tetracaine and were therefore recorded as anesthetic failures.

Only patients with adequate anesthetic conditions after the initial injection of bupivacaine were considered in the determination of the duration of sensory blockade. This duration averaged 104 ± 27 min in the hyperbaric group (n = 14), 128 \pm 23 min in the isobaric group (n = 5), and 127 \pm 25 min in the hypobaric group (n = 3).

After the 30-min study period, during surgical preparation and surgery itself, mean values of central venous pressure and urinary output, when monitored, were comparable in the three groups at all times. The estimated blood loss for all patients was 546 ± 146 mL (hyperbaric), 833 ± 526 mL (isobaric), and 568 ± 342 mL (hypobaric) (no significant differences). Blood transfusions averaged a mean volume of 595 \pm 205 mL in the hyperbaric group (n = 12), 796 ± 443 mL in the isobaric group (n = 13), and 615 \pm 307 in the hypobaric group (n = 10) (no significant differences). The amount of crystalloids administered throughout the study was 2400 ± 520 mL (hyperbaric), 2400 ± 860 mL (isobaric), and 2200 ± 600 mL (hypobaric) (no significant differences).

No postspinal headache was observed in any of 45 patients. One patient in the isobaric group died on the fifth postoperative day of associated major medical problems not related to anesthesia or surgery. Mean duration of hospital stay was 22 ± 10 days, 22 \pm 10 days, and 19 \pm 7 days for the hyperbaric, isobaric, and hypobaric groups, respectively (no significant differences).

Discussion

This study was undertaken to evaluate the anesthetic characteristics of bupivacaine at three different baricities. With the patient in the supine horizontal position at the time of injection, the median height of analgesia obtained after the initial 3-mL (7.5 mg) injection of a hyperbaric solution (T4) was significantly higher than after both the isobaric (T11) and the hypobaric (L1) solutions. Our results are in agreement with the findings of Brown et al. (15), who, in a previous study conducted with tetracaine and using single-injection spinal anesthesia, concluded that when tetracaine was injected at the highest point of the spinal column (i.e., the third lumbar vertebrae), because the hyperbaric solution spread under the influence of gravity, it produced higher sensory levels (T5.5) than did the isobaric (T9.5) or the hypobaric (T10.8) solutions, which remained nearer to the site of injection. Although in our study a different drug was used (bupivacaine, not tetracaine) at a lower dosage (7.5 mg, not 10 and 15 mg) and at a slower speed of injection (1 mL/min, not 2 or 3 mL/15 s), and although conditions of LA drug administration were not identical (CSA in a supine horizontal position, not single-injection spinal anesthesia in a lateral position before turning the patient supine), fairly comparable sensory levels were achieved, suggesting that the intrathecal spread of the three different solutions

Significantly different between hyperbaric and isobaric groups (P <

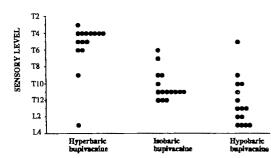
of bupivacaine was similar to the spread of the tetracaine solutions observed by Brown.

A high percentage of patients with inadequate anesthetic conditions 30 min after the initial 3-mL injection of bupivacaine was found in both the isobaric (10/15) and hypobaric (12/15) groups. These patients needed one or two supplemental reinjections of 1 mL (2.5 mg) at 10-min intervals before surgery. All patients in the isobaric group demonstrated a dose-dependent rise in their sensory and motor blockade levels because after a total dose ranging from 10 to 12.5 mg they achieved the required T10 sensory level and a minimum of grade 2 motor blockade.

This finding is in agreement with those of previous studies (15–17), where, during single-injection spinal anesthesia with isobaric bupivacaine used at various concentrations and volumes, the onset, spread, and duration of anesthesia appeared to be primarily related to dosage.

Unlike isobaric bupivacaine, anesthesia in the hypobaric group was unsatisfactory in more than half of the patients (8/15) even after the administration of two additional doses of LAs. In a previous study (12) we radiologically controlled the placement of the intrathecal catheters, which were found to be in the range of T12 to L3 (mean L1); we assumed this to be the case in our present study. Because in the supine position the highest point of the spinal column is L3 and the subarachnoid space is inclined downward in a cephalad direction (18), it is easily understood why there was a poor cranial spread of the hypobaric solution above the presumed level of LA injection in a majority of our patients. The distribution of a hypobaric solution seems, therefore, to depend mostly on posture and on the anatomic configuration of the spinal column, a characteristic similar to that found with hyperbaric solutions. Thus the use of hypobaric solutions of bupivacaine does not seem indicated when hip surgery is planned in the supine position. On the contrary, the same dose of 3 mL (7.5 mg) in the lateral decubitus position has been reported to achieve a mean sensory level of T7-8 with adequate motor blockade in 14 of 15 patients (12).

In the literature, several studies (8–11) using single-injection spinal anesthesia with either isobaric or hyperbaric solutions of bupivacaine and injecting these solutions in either the lateral or the sitting position have commented on the unpredictability of sensory spread, which demonstrated wide ranges of sensory levels as well as high standard deviations. As illustrated in Figure 2, the upper and lower limits of maximum individual sensory levels obtained varied from T3 to L3 in the hyperbaric group (range, 12



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Figure 2. Maximal individual sensory level obtained after the initial 3-mL intrathecal injection in the three groups (n = 15 in each group).

segments), from T6 to T12 in the isobaric group (range, 6 segments), and from T5 to L3 in the hypobaric group (range, 10 segments), demonstrating the considerable scatter of the extent of sensory blockade after a single initial dose of 3 mL (7.5 mg) of bupivacaine. This confirms the inconsistent pattern of spinal spread and the unpredictability of extent of sensory blockade, mainly for the hyperbaric and hypobaric solutions of bupivacaine.

Hemodynamic changes were more severe in the hyperbaric group than in both the isobaric or hypobaric groups (Table 3). This significant difference of decrease in MAP between hyperbaric and isobaric solutions is in agreement with previous findings (5,6).

Although the range of the maximum sensory levels obtained varied greatly in all three groups, a significant negative correlation (simple regression) could be found between the maximal decrease in MAP (percent of baseline value) and the maximal individual level of sensory blockade in all three groups (hyperbaric: r = 0.575, P = 0.025; isobaric: r = 0.688, P = 0.005; hypobaric: r = 0.701, P = 0.004). This finding corroborates the relationship between decrease in MAP and level of sensory blockade found by Pitkānen et al. (10) in his oldest (>80 yr of age) group of patients when he used isobaric bupivacaine under single-injection spinal anesthesia.

In summary, for hip surgery in the supine horizontal position and in elderly patients, isobaric bupivacaine when injected through a catheter during CSA produces a suitable and a more "controllable" anesthesia, but a minimum dosage of 10–12.5 mg is required to obtain adequate anesthetic conditions with moderate decreases in MAP. Because of unnecessary high cephalad spread with major hemodynamic consequences, we believe that hyperbaric bupivacaine should be used only if titrated carefully. Finally, hypobaric bupivacaine, although demonstrating only moderate hemodynamic changes, has a

too great incidence of failure, and its use can be considered in the supine position only for surgery below the hip.

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Absorption and Degradation of Sevoflurane and Isoflurane in a Conventional Anesthetic Circuit

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LIU J, LASTER MJ, EGER EI II, TAHERI S. Absorption and degradation of sevoflurane and isoflurane in a conventional anesthetic circuit. Anesth Analg 1991;72:785–9.

Soda lime and Baralyme degrade sevoflurane, the rate of degradation being a direct function of temperature. We tested whether this degradation would impede the development of an anesthetizing concentration of sevoflurane (compared with isoflurane, a compound that is not degraded) in a circle-absorption system having an increased temperature consequent to (a) carbon dioxide production (200 mL/min) and absorption; and (b) a low inflow rate (70 mL/min). We also measured the temperatures reached in various parts of the absorption system when used in clinical practice, finding that peak temperatures usually reached 37° - 46° C

when low inflow rates (500 mL/min) were applied. The tests in the model system demonstrated that soda lime and Baralyme absorbed both sevoflurane and isoflurane, and that both absorbants degraded sevoflurane but not isoflurane. Baralyme produced a fourfold greater degradation of sevoflurane vapor than did soda lime (0.66 mL/min compared with 0.17 mL/min). However, except for a slight delay at the start of anesthesia, neither absorption nor degradation should noticeably affect the requirement for anesthetic delivery in clinical practice, even in low-flow systems.

Key Words: ANESTHETICS, VOLATILE—sevoflurane, isoflurane. EQUIPMENT, co₂ ABSORBERS.

Sevoflurane is a fluorinated methyl-ethyl ether undergoing testing before possible introduction as an inhaled anesthetic for clinical use. Although it appears to have several advantages over presently available agents (e.g., a pleasant smell, low solubility, minimal effects on heart rate) (1), it is less stable than might be desired. In half-liter flasks containing 100 g of soda lime, sevoflurane breaks down at a rate determined by temperature (2,3). For example, at 40°C, 13% of the amount present at the start of measurement is degraded in the ensuing hour. At 60°C, 56% is degraded per hour. Degradation of isoflurane is not observed at these temperatures.

The implications of these findings for the clinical use of sevoflurane are unclear. Because it likely will be costly, sevoflurane probably will be used in a low-flow or closed circuit system in which the temperature of the absorbant is likely to be increased by the absorption of carbon dioxide. Previous studies

using flasks do not indicate the rate of degradation in a closed or low-flow circuit nor the possible increase in the temperatures of soda lime or Baralyme (Allied Healthcare Products, Inc., St. Louis, Mo.) in such circuits. The present report supplies this information.

Methods

Temperatures Attained in Soda Lime in a Low-Flow System

With approval from the University of California Committee on Human Research, we measured the temperature in soda lime within a conventional absorption system (Ohio model 21 absorber, Ohio Medical Products [presently, Ohmeda], Madison, Wis.). To accomplish this, we put temperature probes (VWR Monitoring Thermometer, 61161-278) in the center of the top, middle, and lower portions of a freshly filled canister placed as the uppermost of the two canisters that comprise the absorption system. The temperature probes were calibrated against a Bureau of Standards mercury thermometer.

Ten patients (eight adults and two children) were studied. Esophageal temperature, body weight, and

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height were measured and patient age noted. Selection of anesthetic agent was determined by the clinician responsible for the patient's care. All patients received isoflurane and nitrous oxide except for two who were given only isoflurane. After induction of anesthesia was completed, we decreased the inflow into the system to the lowest flow (0.50 \pm 0.15 L/min, mean \pm sp) that would maintain the volume in the system during controlled ventilation and concurrent sampling of respired gases for analysis of end-tidal carbon dioxide tension (Perco₂) and anesthetic concentrations. Ventilation was controlled to produce a Perco₂ ranging from 28 to 38 mm Hg (measured by mass spectrometry) in all patients except one undergoing a neurosurgical procedure in whom Perco₂ was maintained at 22 mm Hg. Temperatures were measured for 86-184 min.

Absorption and Degradation of Sevoflurane and Isoflurane in a Standard Low-Flow Anesthetic Circuit: Effect of Soda Lime Compared With Baralyme

A model circuit was prepared using the described Ohio circle-absorption system. The patient's lungs were replaced by a 2-1 Latex bag. Disposable polypropylene corrugated tubing manufactured by Marquest Medical Products, Inc. (Englewood, Colo.) was used to connect the absorbant and valve system to the "lungs." For some of the tests (described below), 200 mL/min of CO₂ was introduced into the bottom of the bag. An Air-Shields Ventimeter Ventilator (Narco Scientific, Air Shields Division, Hatboro, Pa.) provided ventilation sufficient to produce an "end-tidal" CO_2 of 42 ± 2 mm Hg CO_2 , and anesthetics (see below) were measured by a Ramon scattering gas analyzer (Rascal, Albion Instruments, Salt Lake City, Utah). Ventilation was the same when CO₂ was not introduced into the system. An oxygen flow of 70 mL/min was used to compensate for sampling of gases and undetectable leaks from the system. This inflow was sufficient to maintain the ventilator bellows at a full position.

When absorbant was placed in the system, both canisters were filled with either fresh soda lime (Sodasorb, Dewey and Almy Chemical Division, W.R. Grace & Co, Atlanta, Ga.) or fresh Baralyme. With both absorbants, temperature was measured as in the clinical study.

Liquid sevoflurane or isoflurane was injected intermittently into the inspired limb of the circuit in volumes sufficient to maintain the concentration of sevoflurane at approximately 2% and that of isoflurane at approximately 1% in the expired limb. Anesthetic concentrations were measured every 3–6 min with the Rascal device, usually 2 min after injection of agent. Anesthetic was added when the concentration in the expired limb decreased to 1.95% sevoflurane or 0.95% isoflurane.

Six studies were done, each replicated seven times. (1) Sevoflurane was injected in the absence of absorbant or an inflow of CO₂. This, and study 5 (below), served as a control for the effect of loss in overflowing or leaked gases or loss to the plastic components of the circuit (4). (2) Sevoflurane was injected in the presence of soda lime without an inflow of CO₂. (3) Sevoflurane was injected in the presence of soda lime and 200 mL/min inflow of CO₂. (4) Sevoflurane was injected in the presence of Baralyme and 200 mL/min inflow of CO₂. (5) Isoflurane was injected in the absence of absorbant or an inflow of CO₂. (6) Isoflurane was injected in the presence of Baralyme and 200 mL/min inflow of CO₂.

When absorbant was present, the inflow of CO₂ was continued until the temperature in the uppermost layer exceeded 40°C. At this point, the liquid anesthetic was introduced to produce the abovementioned concentrations in a square-wave fashion. These anesthetic concentrations were maintained for the next 2 h by the addition of liquid agent as described.

Using the gas laws, we converted the milliliters of liquid injected into milliliters of vapor injected at room temperature (24°C). For each of the 42 experiments (six studies replicated seven times), we plotted the milliliters of vapor injected as a function of time. We then performed a regression analysis for the data from 20 to 120 min for each experiment. The data from the first 20 min were not included because visual inspection of the plot suggested that this was a period of loading, absorption, and degradation (i.e., requirement was greater during the first 20 min but from 20 to 120 min it assumed a constant value per. minute; an example of this is given as Figure 1). From 20 to 120 min, regression analysis revealed a rectilin ear correlation (r^2 for the six groups equaled 0.991 \pm 0.026—average ± standard deviation). In this report, we define degradation of anesthetic as the breakdown of the parent compound (either sevoflurane or isoflurane); we define absorption as the retention of agent (by soda lime, Baralyme, or circuit components) without degradation. Absorbed agent may subsequently be released.

Statistical analyses were performed to answer the following questions: (a) Did the addition of absorbant increase the amount of anesthetic absorbed? To determine this, we compared the Y intercept for the

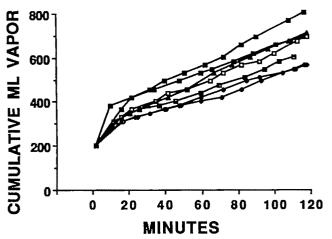


Figure 1. This example graphically displays the cumulative requirement for sevoflurane injection in the 7 studies in group 4 (sevoflurane requirement per 10-min interval vs time; Baralyme absorbant; CO₂ inflowing at 200 mL/min). The increase during the first minute in each graph to 200 mL of vapor resulted from the need to load the system in a square-wave manner. In the ensuing 20 min of measurement, the cumulative rate of ascent of the requirement for sevoflurane injection was less, but still more than after 20 min. We suggest that the requirement during the first 20 min resulted from losses due to both absorption and degradation of sevoflurane. Thereafter the rate of ascent was constant (i.e., a rectilinear requirement existed), and the requirement during this period resulted from the degradation of sevoflurane.

condition achieved with versus without absorbant. (Note that the intercept includes the volume needed to account for both loading of the circuit and absorption by the absorbant. Thus, this comparison will underestimate the actual absorption because of the volume occupied by the absorbant—see Discussion.) (b) Did the addition of absorbant produce degradation of either sevoflurane or isoflurane? To test this, we compared the slopes of the conditions obtained with versus without absorbant. Note that both slopes include the effect of loss of gas from the circuit to compensate for small leaks and sampling of gas. The conditions without absorbant (groups 1 and 5) are the controls for this effect of gas loss through leakage. (c) Did the addition of CO₂ and the consequent increase in absorbant temperature increase degradation? To determine this, we compared the slopes for sevoflurane during conditions including soda lime with versus without addition of CO₂. (d) Was absorption or degradation by Baralyme different from absorption or degradation by soda lime? To test this, we compared the Y intercept and slope for the condition in which soda lime or Baralyme was present and CO2 was added. (e) Finally, did Baralyme result in greater absorption and destruction of sevoflurane than of isoflurane? To determine this, we compared the Y intercept and slope for the conditions including Baralyme, CO₂, and the two anesthetics injected. In each

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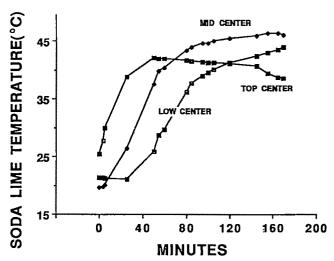


Figure 2. As in this example from a single patient, the temperature of soda lime was measured at the top, middle, and lower layers of soda lime in all 10 patients studied. In all cases, the temperature probe was placed at the center of the soda lime. The patient in this example was 42 yr old, weighed 76 kg, and had a median esophageal temperature of 36.2°C. Inflow was 0.45 L/min. As would be expected, the temperature in the top layer of soda lime reached its zenith earlier than the temperatures in the lower levels because the flow of CO_2 and consequent reaction with soda lime moved from top to bottom.

case, we applied unpaired, two-tailed *t*-tests, accepting a value of P < 0.05 as significant.

Results

Temperatures Attained in Soda Lime in a Low-Flow System

The eight adult patients weighed 73 \pm 18 kg (mean \pm standard deviation) and were 49 ± 14 yr old. The two children weighed 19 and 30 kg and were 4 and 5 yr old, respectively. In our low-flow circuits, temperature increased at all levels of absorbant. The increase initially was greatest in the uppermost portion of the absorber, extending deeper into the absorbant with the passage of time and with exhaustion of the upper layers of absorbant (Figure 2). For normothermic adults (seven of our subjects), the highest temperatures reached ranged from 37° to 46°C (43.5 \pm 3.3°C). For the one hypothermic adult (33.8°C), the highest temperature in soda lime was 33.7°C. In the two children studied, the highest temperatures were 39 and 41°C. Significant positive correlations existed between the highest temperature in soda lime and body weight (temperature = 37 + 0.091 kg; $r^2 = 0.82$) or body temperature (temperature = -137 + 5.1°C; $r^2 = 0.78$).

Table 1. Absorption and Degradation of Sevoflurane and Isoflurane in Soda Lime and Baralyme

	•					
Group	1	2	3	4	5	6
Agent	Sev	Sev	Sev	Sev	Iso	Iso
Concentration (%)	1.99 ± 0.01	1.99 ± 0.01	1.99 ± 0.01	1.99 ± 0.01	1.00 ± 0.01	1.00 ± 0.01
Absorbant	None	Soda	Soda	Bara	None	Bara
CO ₂ *	No	No	Yes	Yes	No	Yes
Maximum temperature (°C)	24.3 ± 1.7	23.3 ± 1.3	48.1 ± 0.5	49.4 ± 0.9	25.5 ± 0.6	48.7 ± 1.5
Intercept (mL vapor·% ⁻¹)	110 ± 9	133 ± 7	125 ± 10	138 ± 22	121 ± 8	147 ± 17
Slope (mL vapor·% ⁻¹ ·min ⁻¹)	0.99 ± 0.13	1.01 ± 0.13	1.16 ± 0.10	1.65 ± 0.30	0.99 ± 0.08	0.70 ± 0.10
Slope difference from group 1 (mL vapor·% ⁻¹ ·min ⁻¹)	0.00	0.02	0.17	0.66	0.00	-0.29

Values are expressed as mean ± sp.

Sev, sevoflurane; Iso, isoflurane; soda, soda lime; Bara, Baralyme. *200 mL/min CO₂ delivered to the circuit.

Absorption and Degradation of Sevoflurane and Isoflurane in a Standard Low-Flow Anesthetic Circuit: Effect of Soda Lime Compared With Baralyme

In the absence of absorbant and CO_2 , the slopes for sevoflurane and isoflurane did not differ (Table 1, comparing values for groups 1 and 5). However, the intercept for isoflurane was slightly higher (P = 0.03). Addition of soda lime significantly increased the absorption of sevoflurane without (comparing intercepts of groups 1 and 2; Table 1; P < 0.001) or with the addition of CO₂ to either soda lime (comparing the intercept for groups 1 and 3; P < 0.01) or Baralyme (comparing the intercepts for groups 1 and 4; P = 0.008). Addition of soda lime in the absence of addition of CO₂ did not produce measurable degradation of sevoflurane (comparing slopes for groups 1 and 2). Addition of CO2 increased the rate of degradation of sevoflurane (comparing slopes for groups 2 and 3; P = 0.02). Baralyme did not absorb significantly more sevoflurane than did soda lime (comparing intercepts for groups 3 and 4). However, the rate of degradation of sevoflurane was greater with Baralyme than with soda lime (comparing slopes for groups 3 and 4; P = 0.001). Baralyme did not absorb more isoflurane than sevoflurane (comparing the intercepts for groups 4 and 6; P = 0.41). However, the rate of degradation of sevoflurane in the presence of Baralyme was greater than the rate of degradation of isoflurane (comparing slopes for groups 4 and 6; P <0.001). Indeed, the slope for group 6 was significantly less (P < 0.001) than the slope for group 5 and the intercept was significantly greater (P < 0.001).

Discussion

We have demonstrated that soda lime and Baralyme, as used in clinical practice, significantly increase the absorption of both sevoflurane and isoflurane. That is, each percentage of agent needed to induce anesthesia in a closed circuit requires an additional 15-28 mL of vapor to compensate for the absorption of the anesthetic agent. Thus, induction of anesthesia with 5% sevoflurane would require the administration of an additional 75–140 mL of vapor. These numbers underestimate the volume absorbed because of the earlier-noted effect of occupation of circuit volume by the absorbant. For example, we estimate the volume of soda lime to be approximately 1070 mL (the filled canisters contain about 2030 g, and soda lime has a specific gravity of 1.86 g/mL). Thus, the above figures should be increased by approximately 11 mL of vapor for each percentage of agent, or by 55 mL of sevoflurane if we assume that induction will require 5% sevoflurane.

Although soda lime absorbs appreciable volumes of sevoflurane, the degradation of sevoflurane is not significant unless CO₂ is added and the temperature of the absorbant increases. Baralyme has a fourfold greater capacity to degrade sevoflurane than does soda lime (compare the values for the last row in Table 1 for groups 3 and 4). In small part, this difference may have resulted from the slightly higher temperature of Baralyme. The average highest temperature reached in group 3 was 48.1 ± 0.6°C compared with $49.5 \pm 1.1^{\circ}$ C in group 4 (P = 0.012). Perhaps the higher temperature with Baralyme resulted from (rather than caused) a greater (exothermic) interaction with sevoflurane, and this heat production added to the heat production from the reaction with CO_2 .

We did not measure the degradation products that might arise from the breakdown of sevoflurane in a closed circuit. This has been done by Hanaki et al., who used a model similar to that applied in the present study (5). In the presence of soda lime and with the introduction of 200 mL/min of CO₂, Hanaki

et al. detected two compounds after providing sevoflurane at a concentration of 2.7%. These compounds had previously been found by Wallin et al., who incubated liquid sevoflurane with soda lime (6). Fluoromethyl-2,2-difluoro-1-(trifluoromethyl)vinyl ether increased to a peak of about 15 ppm by 2 h, slowly decreasing thereafter. Hanaki et al. noted that this compound was anesthetic at a concentration of 3.6% (36,000 ppm) and lethal at a concentration of 10.2% (102,000 ppm). Fluoromethyl-2-methoxy-2,2-difluoro-1-(trifluoromethyl)ethyl ether continued to increase over the total duration of the study, reaching a level of about 2 ppm at 6 h. The toxicity of this compound was said to be unknown. The production of these decomposition products was a direct function of the concentration of sevoflurane in the circuit. Neither Wallin et al. nor Hanaki et al. appear to have measured the decomposition products arising from the interaction of sevoflurane with Baralyme.

Isoflurane, like sevoflurane, is absorbed to Baralyme. However, isoflurane is not degraded by absorbants (consistent with results from previous studies) (3), even when the temperature of absorbant is increased by the addition of CO₂. Indeed, the slope for group 6 was less than the slope for either group 1 or 5. In part, this might be explained by a release of isoflurane from Baralyme as the Baralyme was exhausted by the addition of CO₂. The increase over time in the overall temperature of the Baralyme (i.e., the average temperature of the three layers in which it was measured) also may have decreased the amount of absorbed isoflurane.

The circuit components appear to absorb more isoflurane than sevoflurane (see the difference in intercepts for groups 1 and 5), a finding consistent with the greater solubility of isoflurane in plastics and rubber (4). Although both sevoflurane and isoflurane are absorbed by the rubber and plastic components of the anesthetic circuit and by the alkaline substances used for removal of CO₂, and although sevoflurane is degraded by soda lime and Baralyme, these losses of

agent are of minimal clinical significance. Absorption will influence only the first minute or two of anesthesia. Consider, in addition, the effect of degradation. In the first 30 min of anesthesia, the anesthetist using a closed system containing Baralyme will have to add 19.8 mL of sevoflurane vapor (0.66 mL·min $^{-1}$ ·% $^{-1}$ × 30) for each percent inspired concentration to compensate for the loss by degradation. During this period, a young adult breathing 1% sevoflurane will take up 235 \pm 45 mL (7); that is, degradation would add only 8.4% to the amount of agent that must be added. These values would decrease to 5.1 mL or 2.2% if soda lime were used.

We conclude that absorption and degradation of sevoflurane will not affect the clinical characteristics of sevoflurane. Thus, our data also imply that absorption and degradation should little affect modern or future agents such as desflurane because these are less subject to either loss than is sevoflurane (8).

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Central Cholinergic Depression Reduces MAC for Isoflurane in Rats

Jonathan Zucker, MD

ZUCKER J. Central cholinergic depression reduces MAC for isoflurane in rats. Anesth Analg 1991;72:790–5.

The role of central nervous system cholinergic neuromechanisms during inhalation (isoflurane) anesthesia was evaluated by measuring the minimum alveolar concentration (MAC) in rats before and after selective modulation of cholinergic neurotransmission in the brain. Cholinergic neurotransmission was depressed by reducing synaptic levels of acetylcholine with intracerebroventricular (ICV) injection of the selective anticholinergic hemicholinium-3 and with ICV injection of the presynaptic inhibitory autoreceptor agonist oxotremorine. Hemicholinium-3 (20 μ g) decreased MAC by 18% (P < 0.001), and oxotremorine (20 μ g) decreased MAC by 29% (P < 0.001). Conversely, elevating synaptic levels of acetylcholine and facilitation of

cholinergic neurotransmission by treatment with physostigmine significantly increased MAC. Antagonism of muscarinic receptors with ICV injection of atropine (30 µg) failed to alter MAC, but antagonism of nicotinic receptors with ICV injection of pancuronium significantly decreased MAC in a dose-dependent fashion. The results support the hypothesis that depressed cholinergic neurotransmission in the brain plays a role in the mediation of the anesthetized state. The consequences of depressed synaptic levels of acetylcholine during anesthesia may be mediated through a previously unidentified postsynaptic nicotinic neuromechanism.

Key Words: ANESTHETICS, volatile—isoflurane. BRAIN, CHOLINERGIC MECHANISM—mode of action of anesthetics.

During general anesthesia, the rate of discharge of cholinergic neurons is depressed in several brain regions by a variety of anesthetic agents (1). Volatile anesthetics can interfere directly with molecular events at the cholinergic synapse and membrane environment of the cholinergic receptor (AChR) and elsewhere. For example, they desensitize the acetylcholine receptor (2), alter the binding of acetylcholine with its nicotinic receptor (3), and inhibit the synthesis as well as the release of acetylcholine by inhibiting the presynaptic choline uptake mechanism (4). Additional indirect effects on cholinergic neurons may be shared with intravenous general anesthetics (1,5). For example, GABA-mimetic inhibition at the dendritic origin of cholinergic neurons may decrease their rate of firing and hence decrease the rate of synaptic discharge of acetylcholine at their remote terminal site(s) in the brain (6,7). These observations suggest that depression of central cholinergic neurotransmis-

sion might be one of the mechanisms whereby general anesthetic agents work in the brain to produce the anesthetized state.

It is not uncommon for the same neurotransmitter (in this case, acetylcholine) to have divergent effects on behavior depending on which site is "switched on" by it. For example, whereas microinjection of the cholinergic agonist carbamylcholine into the pontine tegmentum of the cat can produce unconsciousness (8), microinjection of carbamylcholine into the region surrounding the lateral half of the brachium conjunctivum in the cat produces analgesia that is not reversed with naloxone (9). On the other hand, stimulation (or conversely, depression) of neurotransmission in the cholinergic neuronal projection that originates at the medial septum and terminates in the hippocampus antagonizes (or conversely prolongs the duration of) pentobarbital anesthesia (6,10-12). Therefore, depression of cholinergic neurotransmission at one site in the brain might have an effect on anesthesia that is opposite to the effect of depression of cholinergic neurotransmission at another site.

Clinical experience with the "central anticholinergic syndrome" that may occur after general anesthesia (13,14) and perturbations of cholinergic mecha-

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nisms detected in the periphery during general anesthesia (15–18) suggest that central cholinergic mechanisms may be deranged during general anesthesia. We measured the minimum alveolar concentration (MAC) for isoflurane in rats to examine the possible contribution that central cholinergic mechanisms may make to the mediation of general anesthesia. The effect of selected cholinergic and anticholinergic drugs was examined to test the hypothesis that central cholinergic mechanisms might play a role in the mediation of general anesthesia.

Methods

Animals

Two hundred male Sprague–Dawley rats (296 \pm 3.5 g, mean \pm sem) were used in the studies. The study was approved by the University of Washington's animal investigation committee. The rats were housed in the Medical School vivarium and maintained on a 12-h light/dark cycle and provided with food and water ad libitum.

Intracerebral Cannula Implantation

An intracerebral injection guide cannula was implanted in each of the rats at least 7 days before an experiment. This was done after the rats were anesthetized with pentobarbital (35 mg/kg, intraperitoneally [IP]), and a 23-gauge guide cannula was then implanted stereotaxically in the brain and secured to the skull by dental cement and two mounting screws. The tip of the guide cannula was stereotaxically positioned 1.0 mm above the right ventricle. The stereotaxic coordinates of the tip were nose bar -4.0 mm, 1.0 mm posterior to the bregma; 1.5 mm lateral; 2.5 mm ventral from dura, according to the rat brain stereotaxic atlas of Paxinos and Watson (19). At the end of the experiment, 2 μ L of India ink was injected in a similar fashion to the intracerebroventricular (ICV) drug injection, and the animals were given an overdose of pentobarbital and decapitated. Sites of microinjection were later verified by histologic examination of the brains of animals by an observer unaware of the experimental findings. Data from animals without evidence of a clean ICV injection (all the India ink localized to third ventricle) were excluded from the subsequent analysis of intraventricular drug effects.

Intracerebroventricular Drug Administration

Drugs dissolved in sterile pyrogen-free physiologic saline at neutral pH were microinjected into the right

ventricle of anesthetized rats. The injection procedure was as follows: a 30-gauge injection cannula was inserted through the guide cannula to a point 2 mm beyond the tip of the guide cannula in the brain, and drug injection into the cerebrospinal fluid was begun 30 s later at a rate of 2 μ L/min. The injection cannula was removed from the guide cannula 30 s after the injection was completed. In all cases, the volume injected was 1 μ L. Incremental amounts of drug (5, 10, 20, and 30 μ g) were used. Drug treatment was initiated at 5 μ g in a group of experimental animals. If no treatment effect was observed, the experiment was repeated in the next group of animals with the higher dose of the drug.

The following drugs were injected ICV: a-a,dimethylethanolamino-4,4,-bisacetaphone (hemicholinium-3 or HC-3), an analogue of choline that is a specific selective inhibitor of the active presynaptic choline uptake mechanism and a full-spectrum (unrelated to receptor type or subtype) anticholinergic agent that produces global depression of synaptic acetylcholine levels without concomitant depression or activation of other neurotransmitter mechanisms (20); oxotremorine sesquifumarate, a muscarinic AChR agonist with selective action on presynaptic inhibitory M2 autoreceptors, which similarly produces depression of cholinergic synaptic discharge and of synaptic acetylcholine levels (21–23); atropine sulfate, a full-spectrum muscarinic (all subtypes) AChR antagonist (24); pancuronium bromide, a skeletal muscle type nicotinic AChR antagonist with additional antagonist activity at presynaptic inhibitory M2 autoreceptors (24); nicotine sulfate, a nicotinic AChR agonist; or an equivalent volume of saline. All drugs were obtained from Sigma Chemical Company (St. Louis, Mo.).

Determination of MAC

Fifteen hours before the experiment, rats were moved from the vivarium to the research laboratory to be weighed and inspected for any gross evidence of sickness and to be allowed to habituate themselves to the experimental environment. Only healthy rats with a weight gain of 10–15 g during the week after surgery were included in the study. At the start of the experiment the animals were placed in a clear Plexiglas box and exposed to a gas mixture of 5% isoflurane in oxygen until anesthetized 3–4 min later. They were then removed from the box and placed in a specially constructed apparatus that included an oxygen delivery system with an isoflurane vaporizer in line. The gas was delivered to a hollow cylindrical

vessel of 250-mL capacity with a hole in the side near the proximal fresh gas inlet. This hole was sealed with a rubber diaphragm with an aperture that fit over the snout and mouth of a rat. Fresh gas flows of 3 L/min of oxygen were exhausted passively from the distal end. At each anesthetic concentration delivered, the gas in the apparatus was sampled by withdrawal into a glass syringe and then assayed for isoflurane concentration on a calibrated gas chromatograph. Isoflurane concentration in the apparatus correlated closely (r = 0.965, P < 0.001 [two-tailed]) with the concentration of isoflurane set for delivery at the vaporizer. The whole apparatus was housed in a fume hood.

Spontaneously breathing anesthetized rats were placed in the apparatus and exposed to an inspired isoflurane concentration of 2.25% in oxygen for 5 min. The inspired anesthetic concentration was then reduced in a stepwise fashion until MAC for that animal was determined. MAC was determined by the rat's response to the nontraumatic application of a spring-loaded alligator clamp for 2 min at the base of the tail. Purposeful movement of head, trunk, or legs was considered to be a response. Stiffening, hyperventilation, or vocalizing was not considered to be a response. Animals without response had anesthetic concentration reduced stepwise by 0.125% until they responded. After each change in anesthetic concentration, 15 min was allowed for stabilization of the alveolar gas concentrations. Body temperature of the rats was maintained at 37.0°C by a warming blanket attached to a servo mechanism that recorded temperature from a rectal lubricated temperature probe inserted 3 cm.

Once baseline MAC had been determined for each animal, the inspired isoflurane concentration was readjusted to 2.25% and the ICV injections were performed. In some animals, intraperitoneal injections were made at this time of either the cholinesterase inhibitor physostigmine salicylate (0.25 mg/kg) or scopolamine hydrobromide (0.025 mg/kg), a nonselective muscarinic AChR antagonist with limited M2 (cardiac subtype) antagonism; both drugs cross the blood-brain barrier. After the injection, MAC was redetermined. After the final MAC concentration was maintained for 15 min, blood was drawn from the artery at the base of the tail and placed on ice for measurement of blood gas tensions within 10 min.

Data Analysis

Groups of 15-20 animals were allocated for study with each drug manipulation. However, the final

number analyzed in each group varied because of attrition from illness, lost cannulas, and ICV injection sites that were not acceptable. Baseline MAC, MAC after treatment, change in MAC between treatments, and blood gas tensions in the different treatment groups were compared with values in their salinetreated control group by one-way analysis of variance. (Significant differences obtained with this analysis of variance are flagged with asterisks [*].) Additionally, differences between the baseline MAC and MAC after treatment within each treatment group were compared with paired t-tests after confirming normality of distribution of the data. (Significant differences obtained with this paired t-test are flagged with # symbols.) P values of less than 0.05 were regarded as statistically significant.

Results

Baseline MAC for isoflurane in oxygen averaged $1.60\% \pm 0.01\%$ (mean \pm sem). MAC after treatment with ICV saline (n=13) or with sham injections (cannulas were plugged, n=17) was the same as baseline. In contrast, ICV injection of $20~\mu g$ HC-3 (n=13) reduced MAC by 18.1% of baseline (* and #), and ICV injection of $20~\mu g$ oxotremorine (n=17) reduced MAC by 28.7% of baseline (* and #). These data are consistent with a model in which decreased synaptic acetylcholine levels were associated with a decrease in MAC.

The opposite was true for facilitation of cholinergic neurotransmission. Intraperitoneal treatment of the animals with physostigmine (0.25 mg/kg) increased MAC by 14.2% (* and #). The effect of physostigmine on MAC persisted long enough to test whether it could attenuate the effect of HC-3 on MAC. In animals pretreated with physostigmine (0.25 mg/kg IP), baseline MAC was significantly higher (14.3%,*) when compared with all the other groups. After these pretreated animals were injected ICV with HC-3 (20 μ g) or with saline, HC-3 once again reduced MAC by 18.2% of the higher baseline value (* and #).

To examine whether the action of acetylcholine at muscarinic AChR populations might be responsible for the observed change in MAC, the effect of ICV injection of atropine, a full-spectrum muscarinic antagonist, was examined. Atropine (30 μ g, n=11) increased MAC 2.6% above baseline levels. Although this effect on MAC was not statistically significant, the trend toward a higher MAC produced by central muscarinic AChR blockade was supported by the effect of systemic administration of a muscarinic antagonist known to cross the blood-brain barrier.

Table 1. Effect of Treatment on MAC and on Synaptic Acetylcholine Levels

Drug	Synaptic ACh levels	Muscarinic receptors	Nicotinic receptors	MAC Decreased (↓↓)
HC-3	Decreased $(\downarrow\downarrow\downarrow)$	Decreased (indirect)	Decreased (indirect)	
Oxotremorine	Decreased $(\downarrow\downarrow\downarrow)$	M2 agonist (autoreceptor)	Decreased (indirect)	Decreased $(\downarrow \downarrow)$
Physostigmine	Increased (↑↑)	Increased (indirect)	Increased (indirect)	Increased (↑↑)
Atropine	No change (increased?)	Antagonist (full spectrum)	No change	No change (increased?)
Scopolamine	No change	Antagonist (limited M2)	No change	Increased (†)
Pancuronium	Increased (↑)	M2 antagonist (autoreceptor)	Antagonist (skeletal type)	Decreased (↓↓)
Nicotine (low dose)	No change	No change	High-affinity binding	Increased (↑)

ACh, acetylcholine; HC-3, hemicolinium-3.

The effect of treatment with drugs (column 1) on MAC (column 5) is shown, with the number of arrows indicating magnitude of response. In column 2 the expected effect of the drug treatments on synaptic levels of acetylcholine is presented. Also shown are the expected effects the drug treatments are thought to have on muscarinic (column 3) and nicotinic (column 4) receptors. Decreased synaptic levels of acetylcholine expected from treatment with HC-3 and oxotremorine decreased MAC; vice versa for treatment with physostigmine. The consequences of decreased central cholinergic neurotransmission during general anesthesia may be mediated by decreased activity at an unknown type of nicotinic receptor.

Scopolamine (0.025 mg/kg IP, n=9) increased MAC by 8.7% of baseline (*). It is therefore unlikely that the observed changes in MAC seen above with altered synaptic levels of acetylcholine could be due to alteration of cholinergic activity at postsynaptic muscarinic AChR populations in the brain. As expected, ICV injection of 5 μ g pancuronium (n=13) reduced MAC by 7.8% of baseline (* and #). To confirm this effect on MAC, the dose of administered pancuronium was increased as per the experimental protocol. Pancuronium, 10 μ g (n=7), reduced MAC 12.5% below baseline levels (* and #). This dose-dependent effect was confirmed with a 20- μ g pancuronium treatment that reduced MAC by 26.1% of baseline (* and #).

Treatment with nicotine resulted in a triphasic effect on MAC. Intracerebroventricular injection with 5 μ g nicotine increased MAC 9.6% above baseline (* and #). Because there are both high-affinity and low-affinity nicotine binding sites in the brain (25,26), experiments were repeated with incremental doses of the drug. Nicotine, 10 μ g (n=10), did not significantly alter MAC. However, injections with 20 μ g decreased MAC by 10.7% (* and #).

Table 1 summarizes the effect of treatment on MAC, on synaptic acetylcholine levels, and on AChRs. None of the ICV treatments (saline, HC-3, oxotremorine, atropine, pancuronium, or nicotine) produced any significant effect on temperature or arterial blood gas tensions (pH, Pco₂, Po₂, or base excess). Neither did we detect any effect of the

intraperitoneal drug treatments on these measurements.

Discussion

The ICV administration of either HC-3 or oxotremorine decreased isoflurane MAC in rats. Both HC-3 and oxotremorine decrease synaptic levels of acetylcholine. Intraventricular administration of HC-3 reduces levels of brain acetylcholine without changing dopaminergic, adrenergic, or serotoninergic functions (20,27). It does this by selective competitive inhibition for choline at the active uptake mechanism for choline on the presynaptic membrane (28). It thus reduces the availability of cytoplasmic choline, the rate-limiting step in the synaptic turnover of acetylcholine (29). The ICV administration of oxotremorine produces a selective reduction in central cholinergic function by a different mechanism, inhibition of cholinergic synaptic discharge. Oxotremorine is a potent agonist of the muscarinic M2 acetylcholine receptor and acts selectively at presynaptic, inhibitory M2 autoreceptors to limit acetylcholine release (21–24).

Not only do decreased synaptic levels of acetylcholine in the brain during general anesthesia decrease anesthetic requirement, the converse is also true: increased synaptic levels increase anesthetic requirement. Administration of physostigmine significantly increased MAC for isoflurane in rats, presumably by facilitating central cholinergic neurotransmission.

These data are consistent with previous reports on the effects of cholinesterase inhibition and anesthetic requirement (30,31). In rats, ICV administration of neostigmine antagonized the duration of anesthetic action of ketamine and of pentobarbitone without altering the pharmacokinetic profiles of the two anesthetic agents. Interestingly, ICV choline also antagonized the action of the two anesthetics whereas ICV HC-3 markedly prolonged their action (31). The data support the hypothesis that depressed cholinergic neurotransmission in the brain plays a role in the mediation of the anesthetized state.

Postsynaptic actions at either (or both) nicotinic or muscarinic AChRs are potential mediators of the observed effects on anesthetic requirement produced by alterations in synaptic ACh levels. In these experiments, full-spectrum muscarinic antagonism with ICV atropine failed to decrease MAC, whereas systemic administration of scopolamine, an antimuscarinic with limited M2 (cardiac subtype) antagonism, increased MAC. Interpretation of these observations is fraught with pitfalls and may be due to a combination of several factors, which include pharmacokinetic and pharmacodynamic considerations such as presynaptic M2 AChR antagonism with compensatory synaptic ACh release with atropine (22) but not with scopolamine and additional postsynaptic muscarinic inhibitory potentials (24,32). They do, however, suggest that mediation of the overwhelming effects of depressed central cholinergic neurotransmission in the brain during general anesthesia does not involve postsynaptic muscarinic AChR mechanisms. It is tempting to speculate that muscarinically mediated antinociception (9,33) or enhancement of desynchronized sleeplike state (34,35) may be partly responsible for the observed change in MAC produced by the antimuscarinic treatment. Even so, the interplay of these muscarinically mediated central effects would normally be opposed during general anesthesia because of depressed cholinergic synaptic discharge.

Pancuronium, the widely used skeletal muscle nicotinic AChR antagonist, is also a muscarinic M2 (cardiac subtype) AChR antagonist (24). The effect of this drug at presynaptic M2 receptors would be to facilitate synaptic cholinergic discharge and hence to increase MAC by its presynaptic effect. However, ICV administration of pancuronium reduced isoflurane MAC in rats in a dose-dependent fashion. These data indicate a qualitatively and quantitatively relevant effect on MAC mediated through pancuronium-sensitive postsynaptic AChR mechanisms and are consistent with the report (36) of a decrease in halothane MAC in humans given pancuronium intra-

venously. The data suggest that mediation of the consequences of depressed central cholinergic mechanisms during general anesthesia may be through nicotinic postsynaptic AChRs.

Although the role of nicotinic AChRs in neuromuscular transmission is well understood, the role of nicotinic AChRs in brain function is not. Nicotinic AChRs on neurons are part of a gene family that includes nicotinic AChRs on skeletal muscles, chloride ion channels of the GABA receptor complex, and neuronal alpha bungarotoxin binding proteins that in many species, unlike the skeletal muscle nicotinic AChRs, do not have an acetylcholine-regulated cation channel (25). The effect on MAC of treatment with nicotine was triphasic: 5 μ g increased MAC, 10 μ g had no effect, and 20 μ g decreased MAC. This complex response may be due to several different factors, including an interaction of nicotinic AChRs with other neurotransmitter mechanisms such as tachykinins (37) during anesthesia. A more likely explanation might be on the basis of different affinities for nicotine binding at AChR nicotinic subtypes. Binding sites for nicotine in the brain have been described as consisting of two populations (25,26). If so, the data suggest that decreased activity at the high-affinity nicotine binding sites that are also antagonized by pancuronium may play a role in the mediation of the anesthetized state.

The data in this report and reports in the literature (6,8,9,13,31) support the existence of a complex central cholinergic role during anesthesia. Functional depression of cholinergic synaptic discharge characterizes the anesthetized state. During recovery from anesthesia, central cholinergic neurotransmission normalizes. Recovery of the atropine-sensitive central cholinergic arousal system (38) from levels that are depressed during anesthesia may mediate or facilitate the recovery from the anesthetized state (10–12). In contrast, the dominant cholinergic receptor mediating the consequences of decreased available synaptic ACh during anesthesia with isoflurane in rats is probably an as yet unidentified nicotinic subtype.

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Minimal Biotransformation and Toxicity of Desflurane in Guinea Pig Liver Slices

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GHANTOUS HN, FERNANDO J, GANDOLFI AJ, BRENDEL K. Minimal biotransformation and toxicity of desflurane in guinea pig liver slices. Anesth Analg 1991; 72:796–800.

Biotransformation and hepatotoxicity of desflurane were evaluated in the guinea pig liver slice culture system. Liver slices (250–300 µm) were prepared from 600–650-g male Hartley guinea pigs. The slices were incubated in sealed vials in a Krebs–Henseleit buffer at 37°C under 95% O₂. Desflurane was vaporized to produce media concentrations of 0.7–2.3 mM. After incubation (3–24 h) viability of the slices was determined (K⁺ content; protein synthesis/secretion) along with the biotransformation of desflurane

(F⁻). Isoflurane (2.3 mM) was included in the studies for comparative purposes. Although desflurane caused a mild concentration-related reduction in slice K⁺ content (1.1–2.2 mM; 20%–40% of control), the effects were less than those produced by 2.3 mM isoflurane (50% of control). High concentrations of desflurane decreased protein synthesis at the first 9 h of incubation, and isoflurane decreased protein synthesis throughout the incubation period. Neither anesthetic affected protein secretion. The biotransformation of desflurane was minimal with threefold less F⁻ produced from desflurane than isoflurane.

Key Words: ANESTHETICS, volatile—desflurane. BIOTRANSFORMATION (DRUG), DESFLURANE.

Volatile anesthetics are known to result in a low incidence of hepatotoxicity after clinical usage. The guinea pig model has proved to be a good model for the study of anesthetic hepatotoxicity (1). No pretreatment or extensive manipulation (hypoxia or enzyme induction) was required to produce hepatic necrosis by the anesthetics (2). Similar lesions are seen clinically. In this model halothane is metabolized to oxidative intermediates that might be the cause of hepatotoxicity (3). Other volatile anesthetics cause anoxic or ischemic type lesions owing to altered liver blood flow (4). An in vitro guinea pig liver slice model has been developed in our laboratory to study total biotransformation and hepatotoxicity of volatile anesthetics (5) and to focus on the cytotoxicity of the agents in the target organ (6). Furthermore, this system allows detailed mechanistic studies to be performed without confounding systemic influences.

Desflurane (I-653) is a new volatile anesthetic structurally identical to isoflurane (Figure 1) except

that desflurane has a fluorine rather than a chlorine atom on the alpha ether carbon. The properties of desflurane suggests that it may replace isoflurane in some clinical areas. Desflurane has a lower blood gas partition coefficient than isoflurane, which markedly accelerates recovery from anesthesia (7,8). Eger et al. (9) demonstrated that desflurane is relatively free of hepatotoxic, pneumotoxic, or nephrotoxic effects in enzyme-induced, hypoxic rats. When biotransformation was compared with halothane, isoflurane, and methoxyflurane in phenobarbital-pretreated rats, desflurane proved to be relatively stable (10). Desflurane is also reported to be less metabolized than isoflurane in swine (11).

Cultured precision-cut guinea pig liver slices offer a sensitive system to demonstrate hepatotoxic potential and to optimize maximal biotransformation. The objective of this study was to evaluate desflurane using the in vitro cultured guinea pig liver slices and to compare its effects with those of isoflurane.

Methods

Chemicals

Desflurane (I-653) and isoflurane were obtained from Anaquest (Madison, Wis.). L-Leucine-(4,5- 3 H) [53 μ Ci/

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Figure 1. Structural formulas of isoflurane and desflurane.

mmol] was obtained from ICN Biomedicals, Inc. (Irvine, Calif.). Basal medium Eagle amino acids (BME amino acids), basal medium Eagle vitamins (BME vitamins), L-glutamine, and gentamicin were purchased from Gibco Laboratories (Grand Island, N.Y.). Other analytical grade chemicals were obtained from regular commercial sources.

Animals

Adult male Hartley guinea pigs (600–650 g) (Sasco Incorporated, Omaha, Neb.) were housed in stainless steel hanging cages in 12-h light/dark cycles and allowed food and water ad libitum. This strain has shown an incidence of halothane-associated hepatic necrosis of 50% (3).

Preparation of Slices

Animals were killed by cervical dislocation. Livers were excised and immediately placed in 4°C Krebs–Henseleit buffer, pH 7.4 (5,6). Tissue cores (1 cm) were prepared from different areas of the liver lobes, and slices (25–30 mg wet wt; 250–300 μ m thickness) were obtained using a mechanical slicer containing ice-cold Krebs–Henseleit buffer, pH 7.4 (12). Slices were maintained on ice in oxygenated (95% $O_2/5\%$ CO_2) Krebs–Henseleit buffer, pH 7.4, until incubation.

Slice Incubation

Slices were incubated according to the method of Smith et al. (12) and with the modification of Ghantous et al. (5,6). Briefly, three slices were placed on a stainless steel mesh equipped with two stainless steel wheels and then incubated in a glass scintillation vial at 37°C. The vial contained 1.6-mL of Krebs–Henseleit buffer supplemented with BME vitamins, BME amino acids, L-glutamine (1 mM each), and 50 μ g/mL gentamicin (1 mM). Vials were gassed with 95% $O_2/5\%$ CO_2 and incubated for 1 h. The volatile anesthetics were then injected through a Teflon septa cap using a

Hamilton syringe onto a filter paper wick (diameter, 1.2 cm) and allowed to vaporize. Vials were incubated for 24 h on a heated 37°C vial rotator, housed in an acrylic plastic box, and rotated at 3.5 rpm. Slices were removed after 3, 6, 9, 12, and 24 h of incubation and used for measuring the K⁺ level, DNA content, and protein synthesis. The culture medium was collected at the same intervals for measuring protein secretion. In separate experiments the slices and medium were collected together and used for measuring metabolites.

Anesthetic Concentrations

The concentration of the anesthetic was measured in the media (mM) by taking aliquots of medium and extracting with *n*-heptane. The extract was assayed for the anesthetic by gas chromatography (13). Standard curves were prepared by using 0.5–4 mM of different anesthetics in *n*-heptane.

Metabolite Analysis

Samples were combined together after incubation with the anesthetic for 6 h (four vials, each containing three slices and 1.6 mL of media) and lyophylized. The product was dissolved in 600 μ L of distilled water and analyzed for F⁻ content. F⁻ concentrations were measured with an ion-selective electrode (Orion Research, Cambridge, Mass.). Sodium fluoride (1–2 mM) was used for preparing the standard curve. Samples and standards were prepared and carried through the same procedure (14).

K⁺ Content of Intracellular Slice

The K⁺ content of intracellular slices was measured as outlined by Ghantous et al. (5,6). Briefly, slices were removed from the incubation system, blotted, and placed into 1.0 mL of distilled water. Slices were then homogenized by sonication with a Kontes cell disrupter (Vineland, N.J.). After the addition of 50 μ L of bovine serum albumin (50 mg/mL, Sigma Chemical Co., St. Louis, Mo.) and 20 μ L of 70% perchloric acid to 0.4 mL of each sample, the samples were mixed and centrifuged for 10 min at 1400 g. The supernatant fraction was assayed for K⁺ content on a Perkin-Elmer flame photometer (model CA-51, Danbury, Conn.), and the pellet was saved for DNA analysis. A range of standards (0-2 mM KCl) was prepared for calibration. Results were expressed as nmol K+/µg DNA.

DNA Assay

The K⁺ content of slices was normalized to the DNA content of slices measured according to the modified method of Kissane and Robbins (15). Acidified ethanol (3.65 mL of 100% ethanol and 0.1 mL of HCl) was added to each pellet, and the tubes were capped, shaken horizontally for 30 min, and kept at 4°C for 2 h. Samples were centrifuged at 1400 g for 10 min, supernatants were discarded, and pellets were left to dry overnight in a hood. Diamino benzoic acid (0.1 mL of 30% aqueous sol, Aldrich Chemical Co., Milwaukee, Wis.) was added to each tube, the tubes were capped and placed in a 75°C water bath for 35 min, and 1 mL of filtered 1 N HCl was added to the tubes, which were then mixed and read on an Aminco-Bowman spectrophoto-fluorometer (American Instruments Co., Silver Springs, Md.), set at 410-mm excitation and 500-mm emission. Calf thymus DNA (type 1) standards (0–30 μ g) were prepared and carried through the same procedure as the samples.

Protein Synthesis

The slices were incubated in the presence of $0.3~\mu\mathrm{Ci}$ of [$^3\mathrm{H}$]leucine per milliliter of medium, then sonicated in 1 mL of ice-cold 1 N KOH with a Kontes cell disrupter. Aliquots of 50 $\mu\mathrm{L}$ of the slice homogenate were assayed for protein determination (16). An equal volume of 1.5 N acetic acid was added to the rest of the homogenate and centrifuged at 3000 g for 10 min. The pellet was dissolved in 1 mL of 0.5 N NaOH and neutralized by 250 $\mu\mathrm{L}$ of 2 N HCl. The radioactivity was quantified by liquid scintillation counting in 5 mL of Safety-solve (RPI, Mount Prospect, Ill.). Results were expressed as dpm $^3\mathrm{H}$ -incorporated/mg protein (17).

Protein Secretion

Protein secretion was measured in the culture media. Ice-cold 10% perchloric acid (0.2 mL) was added to 1 mL of media, mixed, and centrifuged at 3000 g for 10 min to precipitate the denatured extracellular proteins. The pellet was washed three times by suspending in 2 mL of ice-cold 20% perchloric acid. The final pellet was dissolved in 1 mL of 0.5 N NaOH and then neutralized with 200 μ L of 2 N HCl. The radioactivity was quantified by liquid scintillation count in 5 mL of Safety-solve. Results were expressed as dpm ³H in secreted protein per milliliter of culture media.

Statistics

Experiments were repeated four to five times with slices from different animals. For each experimental condition six slices were used. Thus 24–30 slices were assayed for each experimental point. Values were given as mean \pm standard error of the mean (SEM). Statistical analyses were made using analysis of variance with a Newman–Keuls multiple comparison test.

Results

Anesthetic Concentration in the Media

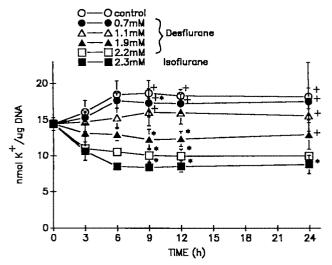
Liquid desflurane (10–60 μ L) was vaporized from the filter paper wick to produce media concentration between 0.7 and 2.2 mM. The high vapor pressure of desflurane made it difficult to handle. The syringes had to be chilled on ice before being loaded with desflurane and kept on ice until injected into the incubation vials. A lower volume of isoflurane (20 μ L) was required to produce a media concentration of 2.3 mM. The differences in the concentration of the different anesthetics are due to their partition coefficients. The level of the anesthetic was maintained throughout the incubation period. Because of the low solubility of desflurane, higher media concentrations were not readily attainable.

Metabolic Production in the Slice

Total F⁻ ion production was measured after incubating the liver slices with 2.3 mM isoflurane or 2.2 mM desflurane for 6 h under 95% O_2 . After isoflurane exposure, F⁻ ion production was 190 \pm 15 pmol F⁻/mg slice wet wt. On the other hand, the guinea pig liver slices produced only 27 \pm 5 pmol F⁻/mg slice wet wt after exposure to 2.2 mM desflurane, which was significantly different from F⁻ production after isoflurane exposure (P < 0.05).

Effect of Desflurane and Isoflurane on Intracellular K⁺ Content

Guinea pig liver slices were exposed to different concentrations of desflurane (0.7–2.2 mM) and 2.3 mM isoflurane for 24 h under 95% $\rm O_2$ atmosphere (Figure 2). Desflurane (1.1–2.2 mM) produced a minor concentration-time related reduction in intracellular K⁺ content of slices (20%–40% reduction from the control). However, this reduction in K⁺ content was less than the



<u>Figure 2</u>. Effect of desflurane and isoflurane on K⁺ content of guinea pig liver slices. Liver slices were incubated with different concentrations of desflurane (0.7–2.2 mM) and 2.3 mM isoflurane for 24 h in 95% O₂. n=15–20 slices from four to five animals. Values are means of nmol K⁺/ μ g DNA \pm sem. *Significantly different from control (P<0.05). +Significantly different from isoflurane (P<0.05).

effect produced by isoflurane, which decreased the intracellular K⁺ content to 50% of control.

Effect of Desflurane and Isoflurane on Protein Synthesis and Secretion in Liver Slices

Initially, the high concentrations of desflurane (1.9 and 2.2 mM) caused a decrease in protein synthesis. However, with further incubation, this proved not to be significant (Figure 3). Isoflurane (2.3 mM) produced a more pronounced decrease in protein synthesis throughout the 24 h of incubation. It should be noted that in earlier studies (18), isoflurane was found to be the least potent volatile anesthetic for inhibition of protein synthesis in liver slices. Desflurane appears to be even less effective than isoflurane. Neither isoflurane nor desflurane had any significant effect on protein secretion by the liver slices (data not shown).

Discussion

When male Sprague–Dawley rats were pretreated with phenobarbital and exposed for 1 h in 12% O_2 to 1.2 MAC of desflurane, isoflurane, or halothane (9), the livers of all rats given halothane had centrilobular necrosis. Isoflurane produced only slight injury. No hepatic injury occurred in rats given desflurane.

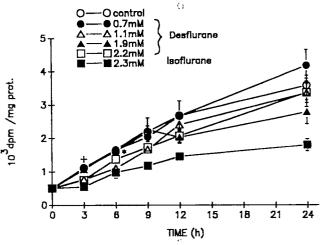


Figure 3. Effect of desflurane and isoflurane on protein synthesis in the guinea pig liver slices. Liver slices were exposed to different concentrations of desflurane (0.7–2.2 mM) and 2.3 mM isoflurane for 24 h in 95% O_2 . Values are means of dpm ³H-incorporated/mg protein \pm SEM. n=15–20 slices from four to five animals. *Significantly different from control (P<0.05). +Significantly different from isoflurane (P<0.05).

Exposing guinea pigs to 1% halothane for 4 h in 21% O_2 produced hepatic necrosis; this occurred without pretreatment or hypoxia (1,2). Under identical conditions, isoflurane did not produce any liver injury in the guinea pig (4). Current opinion is that guinea pigs appear to resemble humans more closely than do rats with regard to acute and mild hepatic dysfunction associated with clinical halothane anesthesia (1,2).

Cultured guinea pig liver slices offer an approach that is suitable to study the biotransformation and toxicity of volatile anesthetics in vitro (5,6). Guinea pig liver slices biotransformed halothane oxidatively and/or reductively depending on the O₂ atmosphere (6). The effects of halothane and other volatile anesthetics on intracellular K⁺ content of the slice and protein synthesis and secretion were studied as indicators of toxicity in this system (6,18). The cultured guinea pig liver slice system could also be used to rank-order the hepatotoxicity of volatile anesthetics (6).

The biotransformation and toxicity of desflurane was examined and compared with the structurally similar anesthetic isoflurane. Desflurane has some similar physical properties to isoflurane (7); however, because of differences in partition coefficients, equal volumes of desflurane and isoflurane, when vaporized from filter paper wicks, resulted in different anesthetic concentrations in the media. This has been demonstrated with other volatile anesthetics too (6). Nevertheless, during incubations the liver slices were exposed to a constant concentration of the volatile anesthetic throughout the incubation period (5).

A previous study has shown that protein synthesis is a more sensitive indicator of the early cellular toxicity produced by mild toxins such as volatile anesthetics than changes in intracellular K⁺ (18). Contrary to this finding, desflurane (2.2 mM) did not produce a significant effect on protein synthesis, yet did decrease the intracellular K⁺ of the liver slices. Isoflurane (2.3 mM) produced significant inhibitions in both these parameters.

K⁺ content of cells is a sensitive index of cell membrane integrity. Loss of K⁺ is most likely due to disruption of the Na⁺/K⁺ adenosine triphosphatase pump (12). However, the effects produced by desflurane on the liver slices could be due, in part, to some of its physical properties. Desflurane has a very high vapor pressure and low solubility in culture medium. To compare the effects of desflurane to isoflurane, liver slices were exposed to similar media concentrations of the anesthetics. Only 20 μ L of isoflurane had to be vaporized for a 2.3 mM medium concentration, whereas 60 μ L of desflurane produced only a 2.2 mM medium concentration. These large volumes of desflurane, when incubated at 37°C in a sealed vial, produced elevated pressures in the vial. The effect of this elevated pressure on the viability of the liver slices is unknown and open for investigation.

Other workers have shown that desflurane is not hepatotoxic in rats and swine (9,11), whereas in the guinea pig liver slice a mild decrease in K⁺ content was observed. In vivo studies with our guinea pig hepatotoxicity model (2) are obviously in order, but will have to await the availability of larger quantities of desflurane for general experimental use.

Compared with isoflurane, desflurane was minimally biotransformed in this system. These results are consistent with the results obtained in rats (9,10) and swine (11) demonstrating that desflurane is minimally biotransformed in intact animals. F⁻ ion production was measured because organic metabolites are not yet reported. The possibility that desflurane undergoes biotransformation to products that covalently bind to tissues remains to be studied. Overall, desflurane is less biotransformed and causes less alterations in liver slice viability markers than isoflurane. Because isoflurane is considered the least hepatotoxic of the currently used volatile anesthetics, desflurane appears destined to assume this role.

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Isoflurane Alters the Kinetics of Oral Cyclosporine

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GELB AW, FREEMAN D, ROBERTSON KM, ZHANG C. Isoflurane alters the kinetics of oral cyclosporine. Anesth Analg 1991;72:801–4.

Cyclosporine is an important immunosuppressive agent often given orally preoperatively to patients undergoing organ transplantation. The aim of the present study was to evaluate the effects of anesthesia on the pharmacokinetics of orally administered cyclosporine. Sixty unanesthetized fasting female Lewis rats were given 25 mg/kg cyclosporine by gastric tube and were then randomized to immediately receive an isoflurane anesthetic (n = 30) or to serve as nonanesthetized controls. At 1, 2, 3, 4, and 6 h after the administration of the cyclosporine, six animals from each group (while still anesthetized for those in the anesthesia group) were killed, and arterial blood and the entire bowel from the esophagogastric junction to the ileocecal junction were removed for measurement of cyclosporine concentrations. A subsequent study with six animals in each group was performed to examine more closely the distribution of cyclosporine in the stomach and small intestine 4 h after the oral dose. In these animals the cyclosporine concentration in the stomach and in five 10-cm-long segments of small bowel was assayed. In all studies of gastrointestinal specimens, the cyclosporine extracted is a combination of that contained in the lumen and the wall.

At all times except at 6 h, the blood cyclosporine levels were significantly higher in the control group than in the isoflurane group. Conversely, the amount of cyclosporine in the distal small bowel of control rats was increased as compared with the anesthetized animals. In the animals studied at 4 h, the amount of cyclosporine in the stomach of control rats was significantly lower than that in the anesthetized animals. Conversely, in the first part of the small bowel, the cyclosporine levels were higher in the isoflurane group.

We conclude from this study that isoflurane anesthesia reduces the rate of absorption of orally administered cyclosporine primarily by reducing gastric emptying and absorption from the proximal small bowel. Similar results may be found with other anesthetics or other orally administered drugs.

Key Words: SURGERY, TRANSPLANTATION. IMMUNE RESPONSE, suppression—cyclosporine.

Cyclosporine is routinely given orally preoperatively for immunosuppression in patients undergoing organ transplantation. It is often given immediately preoperatively so that adequate circulating levels are achieved by the time the new organ is implanted. The effect of anesthesia on the pharmacokinetics of cyclosporine has not been previously studied. The aim of this study was to examine the effect of isoflurane anesthesia on the pharmacokinetics of oral cyclosporine in a rodent model.

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Methods

Sixty fasting female Lewis rats were studied after approval from our institutional review board. The animals were weighed and then given cyclosporine (25 mg/kg) that had been dissolved in olive oil. A 0.3-mL volume was administered by a gastric tube specially designed to be of sufficient length to only reach the stomach. The rats were then randomized either to receive isoflurane anesthesia immediately (n = 30) or to serve as nonanesthetized controls (n = 30). All animals were placed in perspex containers with an orifice at either end that allowed the inflow of 30% oxygen and the outflow of exhaled gas. In the isoflurane group, isoflurane was vaporized in oxygen to give a 1.5% concentration as measured with a Puritan-Bennett infrared gas analyzer. The anesthetized animals were placed on a warming blanket to maintain normothermia.

At 1, 2, 3, 4, and 6 h after the administration of the

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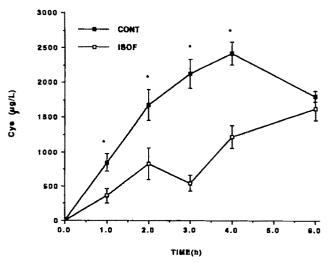
cyclosporine, six animals still anesthetized and six from the control group were killed by cervical dislocation. Arterial blood for measurement of cyclosporine levels was immediately withdrawn from the abdominal aorta into a heparinized syringe. The gastrointestinal tract from the esophagogastric junction to the ileocecal junction was removed, immersed in 10 mL methanol and then cut into small pieces to facilitate extraction of the cyclosporine. After 12 h the methanol was decanted and the cyclosporine extracted twice more into 10-mL volumes of methanol. The latter solution from each animal was pooled and dried under nitrogen. Cyclosporine in whole blood and in bowel extracts was measured by highperformance liquid chromatography (1,2). In all studies of gastrointestinal specimens, the cyclosporine extracted is a combination of that contained in the lumen and that contained in the wall.

A further study of the 4-h time period (n=6 per group) was performed as above to examine more closely the distribution of cyclosporine in the stomach and small intestine 4 h after the oral dose. Four hours was chosen because this was the time of maximum blood cyclosporine concentration in the control group. The gastroesophageal and gastroduodenal junctions were ligated, and the stomach was removed and its cyclosporine content extracted into methanol as described above. The small intestine from the gastroduodenal junction to the cecum was cut into five 10-cm segments (labeled A–E), and the cyclosporine was extracted as described above. The cyclosporine was then assayed and expressed as amount per stomach or per segment.

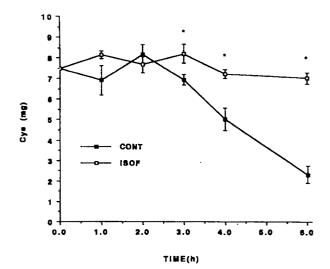
Comparisons of cyclosporine concentrations over time and in the different segments of bowel in the second study were analyzed by analysis of variance and Scheffe's test. At each time period betweengroup comparisons were made by unpaired t-tests. P < 0.05 was considered to be statistically significant. Data are reported as mean \pm sem.

Results

At all times except 6 h, the blood cyclosporine levels were significantly higher in the control group than the isoflurane group (Figure 1). The maximum cyclosporine concentration occurred at 4 h in control animals. However, in the anesthetized animals cyclosporine concentrations continued to rise throughout the study and therefore precluded determination of the peak concentration. Conversely, the amount of cyclosporine extracted from the whole bowel between 3 and 6 h was significantly greater in the



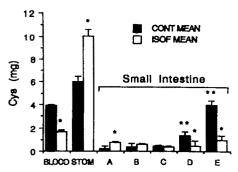
<u>Figure 1</u>. Effect of isoflurane on blood cyclosporine levels in the rat. *P < 0.05 compared with isoflurane. Cont = control.



<u>Figure 2</u>. Effect of isoflurane on cyclosporine content of rat small intestine. *P < 0.05 compared with control.

isoflurane group, indicating a reduced rate of absorption (Figure 2).

The cyclosporine content of blood, stomach, and the segments of small intestine 4 h after the oral dose in the second set of animals is shown in Figure 3. Blood concentrations of cyclosporine were significantly higher in control animals, which confirmed our initial observation. The amount of cyclosporine in the stomach specimens of control rats was reduced as compared with that in the anesthetized animals. Conversely, in the first part of the small bowel specimens (duodenum-jejunum, segment A) cyclosporine levels were higher in the isoflurane group, but more distally (segments D–E) cyclosporine content increased significantly in the control but not in



<u>Figure 3</u>. Cyclosporine content in the blood and digestive tract of the rat. Blood cyclosporine concentration is expressed in milligrams per liter and gut concentration is in milligrams per section. *P < 0.05, isoflurane vs control. **P < 0.05, control group only (D vs E and D or E vs A-C).

the experimental group. In the intervening segments, there were no between-group differences.

Discussion

Cyclosporine is a neutral, lipophilic, cyclic peptide prepared from a fungal extract. The drug reversibly inhibits T cell-mediated immune responses and has revolutionized the success of organ transplantation. For oral administration it is solubilized in an oil vehicle; its absorption from the small intestine of humans and other animals is incomplete and variable (3). Maximum plasma concentrations in humans are usually achieved within 3-4 h. In the blood, most of the drug is associated with lipoproteins and erythrocytes (4,5) and only a small fraction (1%-2%) is unbound. The liver is the major site of cyclosporine metabolism by cytochrome P450 isozymes to more than 20 metabolites, which are excreted primarily in the bile (6–8). Very little cyclosporine is cleared by urinary excretion (6).

We found isoflurane anesthesia to result in significantly lower blood cyclosporine levels during the 6 h of this study. Possible explanations included the following. (a) There may have been an alteration in gut motility so that cyclosporine either did not reach the area of absorption or, alternatively, traversed that region of gut so rapidly that absorption could not take place. (b) Isoflurane anesthesia may have altered the transport or movement of cyclosporine from the gut lumen into the blood. (c) Isoflurane could have reduced gut blood flow thereby reducing absorption. (d) The metabolism of cyclosporine may have been altered by isoflurane.

The second phase of our study entailed a more detailed investigation of the bowel content of cyclosporine. We found that significantly more cyclosporine was still present in the stomach specimens of the anesthetized animals. This is consistent with the observation that anesthesia reduces gastric emptying. The effect of isoflurane on cyclosporine kinetics appears to occur both in the stomach and in the small intestine, as evidenced by the higher stomach and proximal bowel cyclosporine concentrations. Because isoflurane reduces both gastric and small bowel blood flow in rodents this could, therefore, have contributed to the lower blood levels and higher concentrations in the gastrointestinal tract (9). To our knowledge there are no reports on the effect of isoflurane on the transport or movement of substances across the wall of the small intestine. Although the reduction in cyclosporine levels is adequately explained by reduced absorption, we cannot totally exclude an effect of isoflurane on metabolism. However, this is unlikely because the inhalation anesthetics do not cause clinically significant induction of cytochrome P450 isoenzymes (10).

The cyclosporine levels in the specimens of terminal ileum of nonanesthetized animals were found to be significantly higher than those in proximal small bowel specimens. This was not the case in anesthetized rats (Figure 3). Based on pharmacokinetic evidence, Grevel et al. suggested that an absorption "window" exists in the proximal intestine and that more rapid intestinal transit times would decrease the amount of cyclosporine absorbed (11). The observation that cyclosporine accumulated in the distal segments of small intestine of control rats lends support to the concept of an absorption window.

Although we used isoflurane anesthesia, it is possible that our findings would also be obtained with other anesthetic agents and drugs that are known to alter gastrointestinal motility and other mechanisms involved in drug absorption. Furthermore, it is possible that our findings in relation to cyclosporine may also apply to other drugs or substances given orally immediately before induction of anesthesia.

Kinetic observations similar to those seen in the rat have recently been made by Brown et al. in a study of 30 patients undergoing liver transplantation after being given cyclosporine preoperatively (12). Intraoperative blood cyclosporine levels were found to be unexpectedly low when oral doses were given within 4 h of the operation. Although the mechanism underlying their finding was unclear, they assumed it was due to factors that altered absorption and gastric emptying. They recommended that oral doses be given 4–7 h before transplantation. Our study using more frequent sampling during the absorption period confirms their findings that the rate of absorption is

reduced. In addition, our study suggests that delayed gastric emptying is an important factor.

We conclude from this study that isoflurane and possibly other anesthetics significantly reduce the rate of absorption of orally administered cyclosporine primarily by reducing gastric emptying and absorption from the proximal small bowel.

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Use of an Oxygen Concentrator Linked to a Draw-Over Vaporizer (Anesthesia Delivery System for Underdeveloped Nations)

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JARVIS DA, BROCK-UTNE JG. Use of an oxygen concentrator linked to a draw-over vaporizer (anesthesia delivery system for underdeveloped nations). Anesth Analg 1991;72:805–10.

The use of an oxygen concentrator linked to a draw-over vaporizer was examined. The fractional oxygen concentration from this equipment was dependent on the minute ventilation, oxygen output of the concentrator (%), and the presence of an oxygen economizer tube (OET) (a 900-mL corrugated tube). Fractional oxygen concentrations were always higher with an OET than without an OET (other variables being constant).

With the OET in place, the fractional oxygen concentration was only dependent on the minute volume and independent of

the pattern of ventilation (i.e., varying inspiratory and expiratory ratios and inspiratory and expiratory pauses). Without an OET, the performance of the system was considerably impaired. In this setting, the final oxygen concentration depended not only on the added flow of oxygen and minute volume but also on the pattern of ventilation.

In conclusion, when using a draw-over vaporizer linked to an oxygen concentrator, an OET is essential so as to provide consistent oxygen concentrations to the patient at any given minute volume.

Key Words: EQUIPMENT, oxygen concentrator. OXYGEN, concentrators. EQUIPMENT, vaporizers—draw-over.

Today's anesthesiologist should be aware of the existence of, and be acquainted with the function of, oxygen concentrators and draw-over systems used in the modern practice of anesthesiology. Even though these techniques have, at present, limited utility in developed nations, their role is considerable in the field, either for military reasons (1) or in the event of natural disasters. The draw-over systems are of course widely used in underdeveloped nations (2) because of their simplicity, efficacy, and low cost. The linking of an oxygen concentrator (to supply oxygen) to a draw-over anesthetic machine was first described by Fenton in 1989 (3). Although Nunn and colleagues (2) suggested that the addition of an oxygen concentrator would provide the safety of an increased inspired oxygen concentration without dependence on compressed gas, Fenton concluded that this combination represented a significant advance in oxygen availability not only for oxygen for anesthetic delivery systems but for all other hospital use of oxygen as well. The inclusion of the oxygen concen-

trator was considered to improve the safety and the anesthetic capabilities in these places.

In a statement of use of their product, Ohmeda, the manufacturers of the draw-over vaporizer used in this study, states that the device is intended for use in situations where conventional anesthesia equipment is not available. Hence, given the standard of anesthesia care in the United States, the use of a draw-over vaporizer is not appropriate in most situations. Therefore, human studies were not possible in our institution.

This study reports our preliminary results using this equipment in a laboratory with a mass gas monitor to measure the oxygen output of the system, something that neither Fenton nor Nunn and colleagues did, thereby assessing its safety and efficacy. Hence the object of this study was to examine the oxygen output in volume percent from an oxygen concentrator linked to a draw-over vaporizer.

Materials and Method

Essential Components of a Draw-Over Vaporizer

The essential components of a draw-over vaporizer, also called a non-rebreathing demand system, are

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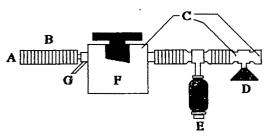


Figure 1. Working diagram of the "PAC" apparatus (for description see text).

displayed in Figure 1. The vaporizer (F) provides an inlet (A) for drawing air in, through a 900-mL corrugated anesthetic tube (B). This tube acts as a reservoir for oxygen and is termed an oxygen economizer tube (OET). From the outlet of the vaporizer, a nonreturn valve (C) is incorporated, and a corrugated anesthetic tube carries the vapor/air mixture to the patient. At the patient's mouth (D), two non-rebreathing valves (C) allow inhalation of only the vapor/air mixture from the inspiratory limb and expiration to the atmosphere. Should controlled ventilation be needed, this can be done by applying positive pressure to the inspiratory limb and can be performed with either a bellows unit (Oxford or Penlon bellows) or a selfinflating bag (Ambu or Laerdal) (E). To prevent gas from passing back through the vaporizer when the bellows or bag is squeezed, a one-way valve (C) must be either incorporated within the bellows or bag or placed at the outlet of the vaporizer. The vaporizer has an inlet for supplementary oxygen (G), also located on the back. This is where the oxygen output tube from the oxygen concentrator is attached. The oxygen concentrator/draw-over combination may now be used without further adjustments. The inspiratory tube may be connected directly to a face mask or to an endotracheal tube. The patient's inspiratory effort draws air over the vaporizer, along the inspiratory tube and into the lungs. The reservoir bag (E) does not collapse because its self-inflating design prevents it from doing so. Expired gases pass out of the exit of the most distal nonreturn valve (C) from the vaporizer into the atmosphere, as shown in Figure 1, or into an expiratory tube that can exhaust the gases out of the operating room. Hence, inflammable or explosive gases need not present a hazard if proper precautions are taken. Diethyl ether is still used to a large extent in underdeveloped countries mainly because it is so inexpensive. During manual ventilation, positive pressure applied to the reservoir bag pushes gas into the patient's lungs because the one-way valve (C) at the vaporizer prevents "back flow" through it. On releasing the bag it reinflates by drawing air and oxygen from the oxygen concentrator over the vaporizer from the OET. The nonreturn valves at the patient's face prevent back flow from the patient along the inspiratory limb while permitting expiration. Thus, to change from spontaneous to manual ventilation merely involves squeezing the bag when required. No other adjustment is necessary. This makes the system very easy to use.

The draw-over vaporizer studied here is part of a PAC Range Portable Anesthesia System produced by Ohmeda (BOC Group, Madison, Wis.). The vaporizer is designed for use over the range of minute volumes normally encountered in draw-over anesthesia, with intermittent flows using ambient air. The vaporizer is temperature-compensated, low-resistance, nonspill, and agent-specific. It can even be operated during transport because its performance is not significantly affected by shaking, by tilting, or even by overturning (4), making it ideal for field conditions.

The Ohmeda Portable Anesthesia System (of which the vaporizer forms a part) is a lightweight (6 kg) portable anesthesia machine. A working diagram of the "PAC" apparatus is shown in Figure 1.

The oxygen concentrator was a Healthaire (Healthdyne, Manetta, Ga.) BX 5000 (115 V). No modification was done to this machine before its use. The concentrator works by having room air pumped by a compressor through one of two canisters containing granules of zeolite that reversibly absorb nitrogen. The canisters are automatically alternately switched, so oxygen is available from one canister while the other regenerates. The principle of this oxygen concentrator is similar to other oxygen concentrators and has been outlined in previous communications (5–7).

The oxygen concentrator avoids electrical and mechanical components and is designed to be maintenance-free and to last for many years. Visual and audio alarms operate in the event of a switching failure, and air is then delivered as the emerging gas. Servicing is required approximately once a year, or after about 9000 h of use. A meter on the front panel records the hours of use. The machine is relatively silent with a modest noise level of approximately 50 dB, which is comparable to a domestic refrigerator. A bacterial filter and a removable humidifier may be provided at the gas outflow point. The controls are simple and comprise an electrical on/off switch for the compressor and a flow-control knob that is set to deliver up to 5 L/min (the European model [220 V] only delivers oxygen up to 4 L/min). One drawback is that there is no lock on the control knob to prevent inadvertent or imprudent unauthorized adjustments once the desired oxygen flow has been set.

The Healthdyne machine weighs approximately 20 kg. It is easily movable because it is fitted with four rotating wheels, and it is approximately 50 cm tall, 30 cm long, and 45 cm wide.

The oxygen output from the oxygen concentrator was attached via a small hose to the vaporizer (G) (Figure 1). The oxygen analysis (concentrations in volume percent) was performed using an Ohmeda 6000 multigas monitor calibrated with air and oxygen. The monitor gas-sampling line was connected via a T-piece distal to the mask connector. The sampled gas was collected continuously at a flow rate of 50 mL/min. No volume correction was made for this loss of volume, nor was there any need to heat the sample tubing to greater than 40°C to prevent condensation of water vapor because there was no water vapor produced. Calibrations were verified frequently during the study, but no changes were necessary because no drifts in performance of the Ohmeda multigas monitor were seen.

The gas flow was measured using the expired minute volume flowmeter on a Servo ventilator 900c (Siemens-Elna, Sweden). The accuracy of the flowmeter at the different mean flow rates (5–25 L/min), with various inspiratory/expiratory ratios and inspiratory and expiratory pauses, was determined using an H7410 calibration syringe (500 mL) (McGraw Respiratory Therapy Research Development Corporation, Valencia, Calif.), and a stopwatch to time the delivery of this volume to the flowmeter. The mean volume recorded by the ventilator flowmeter was within 12 ± 7 mL (mean \pm standard deviation) of the 500 mL, i.e., $2.4\% \pm 1.4\%$ at flow rates within this range (Table 2).

All measurements were recorded at 20°C and 60% humidity. No corrections were made for temperature or humidity and volumes are those recorded by the ventilator, 500 mL having been delivered from the syringe.

Method

The oxygen output in percent from the concentrator was measured at various flow settings (1–5 L/min).

The gas output (in vol%) of the PAC system with the concentrator in circuit was measured during hyper-, hypo-, and normal manual ventilation with 1- or 5-L/min flows of oxygen from the concentrator with or without OET (900 mL). The scavenger outlet of the unidirectional valve was occluded so as to make sure that all inspired gases were measured. The self-inflating bag was manually squeezed and released so that it refilled during the entire expiratory

<u>Table 1</u>. Fractional Oxygen Concentrations Related to Flow From Oxygen Concentrator

O ₂ flow (L/min)	O ₂ concentration	SD	Range	n
1	0.92	0.02	0.85-0.94	22
2	0.92	0.03	0.87-0.94	7
3	0.92	0.03	0.86-0.94	7
4	0.91	0.04	0.85-0.94	7
5	0.91	0.04	0.83-0.97	21

n, number of observations.

<u>Table 2</u>. Volume Calibration Using a Calibration Syringe^a

Approximate flow rate (L/min)	n	Mean volume (mL)	SD	% Error*
5	16	512	2.8	$+2.4 \pm 0.6$
10	17	494	2.1	-1.2 ± 0.4
25	16	492	7.1	-1.6 ± 1.4

The accuracy of the flowmeter of the Siemens-Elna 900c at different mean flow rates between 5 and 25 L/min was determined using a 500-mL calibrated syringe and a stopwatch to time the delivery of this volume to the flowmeter. These measurements were all recorded at 20°C and 60% humidity, and volumes are those recorded by the ventilator, 500 mL having been delivered from the syringe. The mean volume recorded by the ventilator flowmeter was within 12 \pm 7 mL (mean \pm sp) of the 500 mL, i.e., 2.4% \pm 1.4% at the flow rates within this range. (No correction was made for the small deviation of the flow transducer.)

% Error =
$$\frac{\text{Mean recorded volume} - 500}{500 \text{ mL}} \times 100.$$

period by retarding the self-inflation. The inspiratory and expiratory ratios were timed using a metronome.

Measurements of the final fractional oxygen concentrations were taken only after stable readings were achieved.

Results

The oxygen output of the concentrator (by itself), in percent related to flow, is shown in Table 1. The oxygen output, varying between 91% and 92%, showed greater (scatter) variability at higher flows, but with an insignificant lower mean value. No corrections were made for the small deviations of the flow transducer.

The fractional oxygen concentration from the PAC system linked to the oxygen concentrator was dependent on the minute ventilation, oxygen output of the concentrator, and the presence of the OET (Figure 2). With an OET in place (900 mL), fractional oxygen concentrations were always higher than those obtained with no OET (other variables being the same). As expected, when a lower flow of oxygen was

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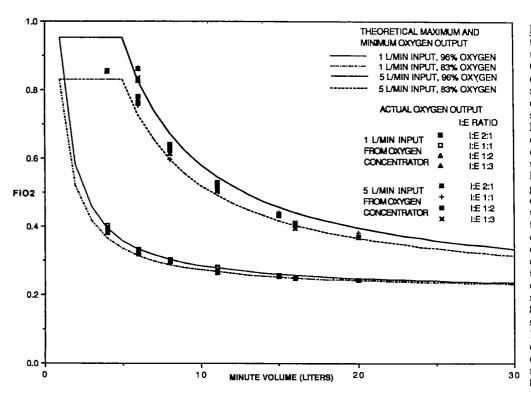


Figure 2. Oxygen concentration (Fio2) versus minute volume (liters) with the use of the OET at various inspiratory/ expiratory (I/E) ratios and flow rates of 1 and 5 L/min from the oxygen concentrator. The results lie close to or within these limits and demonstrate that the oxygen concentration from the circuit depends on minute volume and is independent of the I/E ratio of ventilation for a given input flow from the concentrator into the circuit. The upper pair of lines show the theoretical fractional oxygen concentration limits from the circuit assuming an input flow of 5 L/min from the concentrator with a maximum oxygen concentration of 96% and a minimum concentration of 83%. The lower pair of lines are similarly for an input flow of 1 L/min from the oxygen concentrator with a maximum concentration of 96% and a minimum concentration of

supplied to the circuit from the oxygen concentrator, lower fractional oxygen concentrations were observed. The fractional oxygen concentrations were, furthermore, only dependent on the minute volume and were independent of the pattern of ventilation when the OET was in place. The pattern of ventilation, i.e., varying inspiratory and expiratory ratios and inspiratory and expiratory pauses, made no difference to the final fractional oxygen concentrations. When lower minute volumes are used, less air is drawn into the circuit to dilute the oxygen input from the concentrator and thus higher fractional oxygen concentrations are observed.

Without an OET, the performance of the system was considerably impaired (Figures 3 and 4). The final fractional oxygen concentration depended not only on the flow of oxygen and minute volume, but also on the pattern of ventilation. With no dead space to collect the oxygen from the concentrator, oxygen is drawn into the circuit during inspiration in the spontaneous ventilation mode and during "expiration," i.e., when the self-inflating bag refills in the controlled-ventilation mode (Figure 1). The vaporizer performance was similar to that seen in other studies (4).

Discussion

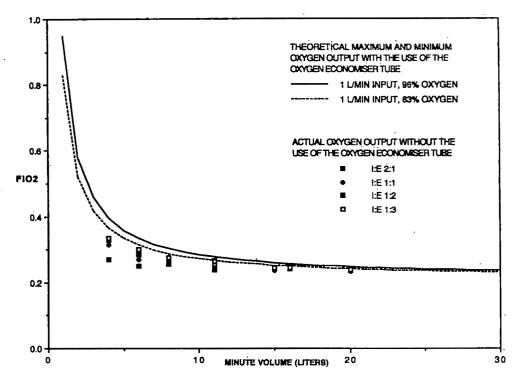
The Healthdyne oxygen concentrator and the Ohmeda draw-over vaporizer would seem to be a safe

and reliable alternative to usual modern anesthetic systems. Manual ventilation (hypo-, normal, or hyperventilation) produced a consistent gas output in a safe range.

The use of oxygen concentrators for home patients who require high inspired oxygen concentration is well-established. It eliminates the problems associated with cylinder changing and limited supplies. It is also much simpler to operate and less hazardous than systems using pressurized cylinders. The oxygen concentrators would seem to be advantageous as a potential source of oxygen in rescue helicopters, ambulances, major disaster areas, and, of course, military conflicts.

The oxygen concentrator would seem to have a particular application in developing countries where delivery of oxygen cylinder supplies is often infrequent, unreliable, and sometimes nonexistent. The linking of an oxygen concentrator to an anesthetic machine would, therefore, be an obvious choice under these circumstances. It may also prove to be valuable in more sophisticated centers, to provide oxygen in patient areas where there are no pipeline supplies or during deliberate or accidental hospital oxygen pipeline shut-off. Large-scale oxygen concentrator installations have been used to provide complete hospital pipeline systems (8).

The possible hazards of oxygen concentrators are few, but, obviously, normal practice of electrical safety is imperative. The concentrator must be placed



 $\frac{\text{Figure 3}}{(\text{Fio}_2)}$. Oxygen concentration $\frac{\text{Fio}_2}{(\text{Fio}_2)}$ versus minute volume (liters) without the use of the OET tube at various inspiratory/expiratory ratios and an input flow of 1 L/min from the oxygen concentrator.

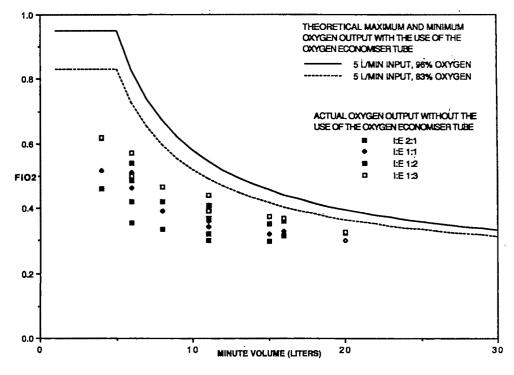


Figure 4. Oxygen concentration (Fio₂) versus minute volume (liters) without the use of the OET at various inspiratory/expiratory ratios and an input flow of 5 L/min from the oxygen concentrator.

in such a position that the in-draw area is unlikely to be contaminated with atmospheric pollutant because this calls for partial exhaustion of the zeolite cylinder (9). There has also been a report from the same reference of sudden failure of the oxygen concentrator device attributed to a failure of the valve linking the two cylinders. The provision of a bacterial filter at

the outlet combined with the use of dust-free zeolite should exclude the possibility of particle contamination of the delivered gas. Other oxygen concentrators may also suffer from compressor faults (10) and excessive noise (11).

From Figure 2 it can be seen that with an oxygen economizer tube (900 mL), the oxygen concentration

conformed closely to the predicted curve and was, furthermore, independent of the pattern of ventilation. It was fairly easy to obtain stable minute volumes with manual ventilation within 0.5 L/min of the desired volume.

In summary, it is essential that, when one is contemplating using this equipment, an OET with a volume of 900 mL be incorporated with the vaporizer (Figures 1, 3, and 4). The concentration of oxygen in the absence of an OET is low and unpredictable, varying with both the pattern of ventilation and minute volume.

We, therefore, believe that the oxygen concentrator coupled with the draw-over vaporizer with an OET can give a safe and reliable gas concentration of oxygen independent of the pattern of ventilation. Hence, linking this vaporizer to an oxygen concentrator could prove expedient, safe, and useful in underdeveloped nations, military conflicts, ships at sea, aircrafts, and disasters in remote areas where oxygen cylinder stockpiling is not indicated. Based on our results we will consider requesting Ohmeda to change the statement of use of the PAC unit so that it can be used in appropriate U.S. teaching hospitals where conventional anesthesia equipment is available. It is imperative that specialized anesthesiologists, even in the United States, become acquainted with this mode of anesthesia delivery, as they may easily find themselves in a situation where a drawover vaporizer may be the only anesthetic alternative. Is it fair to ask people to administer anesthesia using a system to which they have not been exposed, or with which they are totally unfamiliar?

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Dose-Response Relation, Neuromuscular Blocking Action, Intubation Conditions, and Cardiovascular Effects of Org 9273, a New Neuromuscular Blocking Agent

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VAN DEN BROEK L, LAMBALK LM, RICHARDSON FJ, WIERDA JMKH. Dose-response relation, neuromuscular blocking action, intubation conditions, and cardiovascular effects of Org 9273, a new neuromuscular blocking agent. Anesth Analg 1991;72:811–6.

The ED $_{50}$ and the ED $_{90}$, the time-course of the neuromuscular block, the intubation conditions, and the cardiovascular effects of Org 9273, a new steroidal nondepolarizing neuromuscular blocking agent, have been evaluated in 41 anesthetized patients. From cumulative dose-response curves the ED $_{50}$ and ED $_{90}$ were calculated to be 175 and 300 μ g/kg, respectively. The time-course of neuromuscular blockade after 300- and 500- μ g/kg doses of Org 9273 appeared to be similar to that of equipotent doses of

vecuronium. The neuromuscular block was characterized by a fast initial rate of block development. High-dose Org 9273 (1 mg/kg = 3-4 times the ED $_{90}$) had a clinical duration comparable to an intubating dose of pancuronium, but a considerably more rapid onset and recovery index. Three hundred micrograms per kilogram and 500 µg/kg Org 9273 produced good to excellent intubation conditions 1 min after administration. Org 9273 in a dose of 0.5-2 times the ED $_{90}$ produced no cardiovascular changes; however, 3-4 times the ED $_{90}$ increased heart rate 20%–25% (P < 0.001), probably due to a vagolytic effect.

Key Words: NEUROMUSCULAR RELAXANT, Org 9273.

As a result of the search for a nondepolarizing neuromuscular blocking agent as an alternative to succinylcholine for intubation and short surgical procedures, some new neuromuscular blocking agents have recently become available for clinical trials. One of these agents is Org 9273, the 2-morpholino, 3-desacetyl analogue of vecuronium (Figure 1), which has been shown to be stable in aqueous solution.

Preliminary animal studies (1,2) show that Org 9273 is 3–5 times less potent than vecuronium but with a faster onset of action and a similar duration of action. Furthermore, Org 9273 in doses of 1–3 times the ED₉₀ produces only minor changes in heart rate and blood pressure in experimental animals.

We have performed a dose-finding study to investigate the dose-response relationship, the time-course

of neuromuscular blocking action, the intubation conditions, and the hemodynamic stability of Org 9273 in anesthetized patients.

Methods

The study was approved by the local medical ethical committee. Forty-one ASA physical status I and II patients, aged 18–60 yr, scheduled for elective surgery, participated in this study after they had given written informed consent.

After oral premedication with 7.5 mg midazolam approximately 60 min before the expected start of anesthesia, anesthesia was induced with 1–5 μ g/kg fentanyl and 3–7 mg/kg thiopental. After tracheal intubation, anesthesia was maintained with halothane, 0.5% inspiratory concentration, in a 2:1 mixture of nitrous oxide and oxygen and increments of 50–100 μ g fentanyl. End-tidal Pco₂ was kept between 32 and 42 mm Hg. After \geq 90% recovery from the Org 9273 block, vecuronium was used to maintain muscle relaxation if necessary. Central and peripheral

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Figure 1. The chemical structures of Org 9273 and vecuronium.

temperatures were kept above 36.5 and 32.5°C, respectively.

Heart rate and arterial blood pressure were measured noninvasively (Dinamap, Criticon, Tampa, Fla.) each minute, starting before the induction of anesthesia and ending 15 min after the administration of Org 9273. The end-tidal Pco2 and the electrocardiogram were monitored continuously (Cardiocap, Datex, Helsinki, Finland). Neuromuscular transmission was monitored immediately after induction of anesthesia. The preload was kept constant between 200 and 300 g, and contractions of the adductor pollicis longus muscle were measured isometrically after stimulation of the ulnar nerve at the wrist through surface electrodes. The supramaximal stimulus was determined, and the system was allowed to stabilize, which usually took 3-5 min. Supramaximal stimuli of 0.2-ms duration were administered at a rate of 0.1 Hz with a Grass S88 nerve stimulator (Grass Instruments, Quincy, Mass.). The resultant force of thumb adduction was quantitated by a force-displacement transducer (Statham UC3 [Gould-Statham, Oxnard, Calif.]) and recorded (Gould 220 Brush recorder [Gould, Cleveland, Ohio]). Monitoring was continued until more than 90% recovery of single twitch response had occurred.

After stabilization of anesthesia and the twitch response, the selected dose of Org 9273 was administered in a constant volume (10 mL) of saline over 10 s into a fast-running intravenous infusion. The dose was based on the corrected body weight (CBW):

$$CBW = [Height - 100] + \frac{Weight - [Height - 100]}{2}$$

where CBW and weight are given in kilograms and height is given in centimeters. Eleven patients (patients 1–11) received maximal 3–4 cumulative doses within 10–12 min for linear regression analysis of the dose-response curve using log-logit transformation; the $\rm ED_{50}$ and the $\rm ED_{90}$ of Org 9273 were derived from the linear regression equation.

For evaluation of the time-course of the neuromuscular blocking action, 12 patients (patients 12–23) were given 300 μg/kg of Org 9273, the estimated ED₉₀, 8 patients (patients 24–31) received 500 μ g/kg, and 10 patients (patients 32–41) received 1000 μ g/kg. From the recorded single twitch-response the following variables were calculated: (a) the lag time (time from the end of injection of Org 9273 until the first depression of the twitch response); (b) the magnitude of the neuromuscular block at 1 min after the injection of Org 9273; (c) the maximal neuromuscular block (0%-100%); (d) the onset time (time from the end of injection of Org 9273 until the maximal depression of the twitch response); (e) the duration of effect (time from the end of injection of Org 9273 until 25% recovery of the twitch response) (Dur 25); (f) the recovery-index (time from 25% to 75% recovery of the twitch response); and (g) the duration from the end of injection of Org 9273 until 90% recovery of the twitch response (Dur 90). In 14 patients, intubation conditions 1 min after the end of the injection of Org 9273 were evaluated according to the scale of Krieg et al. (3) (a 12-point scoring system related to three different parameters: position and reaction of vocal cords, presence of coughing, and ease of laryngoscopy; 3 = optimal intubation conditions, 12 = impossible to intubate). Six patients (patients 12–17) were given 300 μ g/kg and 8 patients (patients 24–31) received 500 μ g/kg. The degree of neuromuscular blockade at the time of intubation was registered.

All patients were monitored for possible cardiovascular effects from Org 9273. In addition, these effects were studied before intubation in 10 patients after the administration of 1000 μ g/kg Org 9273 (3–4 times the ED₉₀). The cardiovascular variables after the administration of Org 9273 were compared with postinduction values.

Paired analysis of variance was applied to compare cardiovascular measurements obtained in time with baseline values. Significance was defined at the P < 0.05 level.

Results

Log-logit transformation yielded a regression line with a slope of 4.06 (R value 0.988) and an intercept

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<u>Table 1</u>. Lag Time, Neuromuscular Block at 1 Minute (NMB1), Maximal Neuromuscular Block (NMB2), Onset Time, Clinical Duration (Dur 25), Recovery Index, Total Duration (Dur 90) (n = 12), and Intubation Conditions (intub score) (n = 6) After 300 μ g/kg Org 9273 in Anesthetized Patients

Patient No.	Lag time (s)	NMB1 (%)	NMB2 (%)	Onset time (min)	Dur 25 (min)	Recovery index (min)	Dur 90 (min)	Intub score
12	24	60	97	4.4	22	8	31	4
13	60	65	96	2.7	18	9	32	4
14	60	5	96	3.0	22	13	41	3
15	36	58	86	2.8	19	8	28	3
16	36	60	96	3.0	17	10	32	5
17	60	40	96	3.7	22	8	33	5
18	36	62	92	2.8	10	6	19	Wherear
19	24	90	96	2.3	12	8	21	-
20	36	40	86	5.1	17	11	31	MANAGEMENT
21	48	65	91	3.8	17	9	29	
22	36	60	97	4.0	16	11	32	
23	24	87	96	3.3	15	6	26	Anna
Mean	40	57	94	3.4	17	9	29	4.0
SD	14	22	4	0.8	4	2	6	0.9

Table 2. Lag Time, Neuromuscular Block at 1 Minute (NMB1), Maximal Neuromuscular Block (NMB2), Onset Time, Clinical Duration (Dur 25), Recovery Index, Total Duration (Dur 90), and Intubation Conditions (intub score) After 500 μg/kg Org 9273 in Anesthetized Patients

Patient No.	Lag time (s)	NMB1 (%)	NMB2 (%)	Onset time (min)	Dur 25 (min)	Recovery index (min)	Dur 90 (min)	Ințub score
24	48	87	98	2.8	30	5	37	3
25	4 8	<i>7</i> 2	100	2.0	22	8	31	3
26	36	<i>7</i> 5	100	2.5	26	6	35	3
27	36	100	100	1.0	38	15	58	3
28	36	94	99	2.0	29	5	37	3
29	36	94	99	2.0	28	13	46	3
30	36	96	100	1.5	39	11	- 58	3
31	36	87	100	1.5	23	4	39	4
Mean	39	88	99	1.9	29	8	42	3.1
SD	5	10	1	0.6	6	4	10	0.4

Table 3. Lag Time, Neuromuscular Block at 1 Minute (NMB1), Maximal Neuromuscular Block (NMB2), Onset Time, Clinical Duration (Dur 25), Recovery Index, and Total Duration (Dur 90) After 1000 μ g/kg Org 9273 in Anesthetized Patients

Patient No.	Lag time (s)	NMB1 (%)	NMB2 (%)	Onset (min)	Dur 25 (min)	Recovery index (min)	Dur 90 (min)
32	24	92	100	1.8	78	23	109
33	48	92	100	2.0	37	8	47
34	24	<i>7</i> 5	100	1.7	<i>7</i> 2	17	95
35	48	38	100	2.7	48	9	60
36	24	100	100	0.7	101	41	149
37	36	100	100	1.0	55	13	74
38	36	100	100	0.8	66	20	93
3 9	24	100	100	1.0	41	9	58
40	36	100	100	0.8	52	20	85
41	24	100	100	0.5	76	36	119
Mean	32	90	100	1.3	63	20	89
SD	10	20	0	0.7	20	11	31

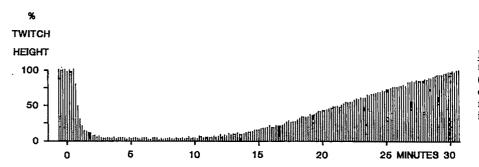


Figure 2. Twitch response (0.1 Hz) after the administration of 300 μ g/kg Org 9273 (patient 21). The neuromuscular block is characterized by a short lag time and a rapid initial rate of development, resulting in a 65% block at 1 min.

of -9.09. The ED₅₀ and ED₉₀ values were 175 and 300 μ g/kg, respectively.

The magnitude and time-course of the neuromuscular block and the time-course produced by 300, 500, and 1000 μ g/kg Org 9273 are presented in Tables 1, 2, and 3, respectively. The neuromuscular blocks were characterized by a short lag time and a rapid initial rate of development, resulting in considerable neuromuscular block 1 min after the administration of Org 9273. A typical example of a registration is shown in Figure 2.

The mean (SD) intubation score was 4.0 (0.9) and 3.1 (0.4) at 1 min after 300 and 500 μ g/kg, respectively (Tables 1 and 2). In the 300- μ g/kg group (n=6), 2 patients had excellent intubation conditions, 4 patients reacted with minor diaphragmatic coughing, and in 2 patients the vocal cords were not completely motionless during intubation. Tracheal intubation performed 1 min after 500 μ g/kg Org 9273 (n=8) was always characterized by easy laryngoscopy with vocal cords abducted and motionless. Minor diaphragmatic coughing developed in only one patient and that was mild. The mean (SD) neuromuscular block at the time of intubation was 48% (22) after 300 μ g/kg Org 9273 (patients involved in the intubation study) and 88% (10) after 500 μ g/kg.

Heart rates and the systolic and diastolic blood pressures before and after the administration of 1000 μ g/kg Org 9273 are presented in Figure 3. Org 9273 increased the heart rate 20%–25% (P < 0.001) without significant changes in systolic and diastolic blood pressure.

Discussion

From our results we conclude that Org 9273 has approximately 15%–20% of the potency of vecuronium (Table 4).

Calculation of the ED_{50} and ED_{90} using cumulative dosages of short-acting drugs may yield slightly higher values than when using single-bolus doses (4),



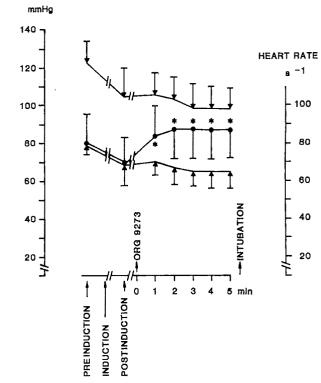


Figure 3. Systolic (\P) and diastolic (\triangle) blood pressures and heart rate (\bigcirc) after the administration of 1000 μ g/kg Org 9273 [mean (sD)]. P values for the comparison of postinduction values with values after the injection of 1000 μ g/kg Org 9273. *P < 0.001.

so that the actual ED_{50} and ED_{90} of Org 9273 are probably lower than 175 and 300 μ g/kg, respectively.

Org 9273 has a time-course of action similar to that of vecuronium and Org 9426. After 3–4 times the ED₉₀ dose, the onset is more rapid and the clinical duration is slightly shorter than that of 80 μ g/kg pancuronium (Table 4).

An intriguing finding in our study was the short lag time and rapid initial rate of block development, which was also found after the administration of Org 9426, another new steroidal muscle relaxant with a potency similar to Org 9273 (6). These findings could be due to pharmacokinetic factors (e.g., rapid initial

 $\underline{\text{Table 4}}$. $\mathrm{ED_{90}}$ Ratio, Lag Time, Maximal Neuromuscular Block (NMB_{max}), Onset Time, and Clinical Duration (Dur 25) After Different Doses of Four Different Neuromuscular Relaxants

Drug	n	Dose (μg/kg)	ED ₉₀ ratio	Lag time (s)	NMB _{max} (%)	Onset (min)	Dur 25 (min)	Ref*
Vecuronium	8	50	1		95 ± 6	4.7 ± 0.8	13.6 ± 3.3	3
Vecuronium	8	100	2		100 ± 0	2.4 ± 0.6	-	5
Org 9273	12	300	1	40 ± 14	94 ± 4	3.4 ± 0.8	17 ± 4	
Org 9273	8	500	1.5-2	39 ± 5	99 ± 1	1.9 ± 0.6	29 ± 6	
Org 9273	10	1000	3-4	32 ± 10	100 ± 0	1.3 ± 0.7	63 ± 20	
Org 9426	11	250	0.75	34 ± 11	69 ± 22	3.8 ± 1	5 ± 5	6
Org 9426	11	500	1.5	36 ± 14	98 ± 3	3.4 ± 1.2	21 ± 5	6
Pancuronium	10	80	2	36 ± 9	99.6 ± 0.2	_	86 ± 41	7

^{*}Comparison of results of this study with other studies (Ref = Reference) under comparable anesthetic conditions.

clearance) and/or pharmacodynamic factors (e.g., early inhibition of presynaptic nicotinic cholinoreceptors) (8). Another explanation is that, because of the low neuromuscular blocking potency, a large number of drug molecules produces a large initial gradient between the plasma and the site of action. Thus, the law of mass action (9) might explain the rapid onset.

Org 9273 might be an alternative for succinylcholine, especially in patients in which succinylcholine is contraindicated and a rapid intubation has to be achieved. Three hundred micrograms per kilogram Org 9273 ($\pm ED_{90}$) produces good to excellent intubation conditions after 1 min and a short clinical duration of action (Dur 25: 17 \pm 4 min), and would be potentially useful for short procedures. Five hundred micrograms per kilogram Org 9273 (1.5–2 times the ED_{90}) produces excellent intubation conditions after 1 min at the cost of a slightly longer clinical duration (Dur 25: 29 \pm 6 min) and might be suitable for rapid sequence induction.

The discrepancy between the good to excellent intubating conditions after 1 min after the administration of Org 9273 and the far-from-maximal neuromuscular block of the adductor pollicis longus muscle at the same time might be explained by a faster onset of neuromuscular blockade of the laryngeal muscles owing to differences in pharmacokinetic and pharmacodynamic factors. This phenomenon was demonstrated by our group in cats (10) and by Donati et al. and Meistelman et al. in humans (11,12). Another factor influencing the intubation conditions is the depth of anesthesia. This study was not placebocontrolled; Baumgarten et al. (13) have already shown that, under comparable anesthetic conditions, intubation after a placebo is either very difficult or impossible.

In the first (dose-finding) part of the study, in which doses up to 2 times the ED₉₀ were given, we observed no cardiovascular changes that could be related to the drug under investigation. Evaluation of

the cardiovascular effects (in the absence of intubation) after 3–4 times the ED₉₀ of Org 9273 demonstrated a 20%–25% increase in heart rate, which is comparable to changes in heart rate after an intubation dose of pancuronium (14). This probably represents a vagolytic effect (2). In the opinion of a number of anesthesiologists, such an increase in heart rate might be useful to compensate for the decrease in heart rate often seen after the administration of opioid drugs (15) or during surgical stimulation (16), especially in combination with vecuronium. A relaxant inducing a slight increase in heart rate could have clinical advantages, and might be preferred to the available vagolytic drugs, which are unpredictable as to effect and produce unwanted side effects.

To determine the position of Org 9273 in daily practice more precisely, further studies are necessary to confirm these preliminary results and to evaluate possible cumulative properties, reversibility, and interactions.

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Case Reports

Cauda Equina Syndrome and Continuous Spinal Anesthesia

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Key Words: ANESTHETIC TECHNIQUES, SPINAL. ANESTHETICS, LOCAL—lidocaine, bupivacaine. COMPLICATIONS, NEUROLOGIC—cauda equina syndrome. TOXICITY, NEUROTOXICITY.

Recently, Kendall Health Care Products Company issued a precaution concerning continuous spinal anesthesia using the Cospan spinal catheter after receiving reports of neurologic deficits associated with continuous spinal anesthesia characterized by perineal sensory loss and changes in sphincter function. Similarities in these reports include (a) the use of 5% lidocaine in 7.5% dextrose (50 mg/mL); (b) less than the expected anesthetic effect for a given dose; (c) an initial lidocaine dose of 100 mg or more to establish the spinal anesthetic; and (d) a total lidocaine dose exceeding 100 mg. Because of these similarities, the company recommended that (a) the spinal catheter not be threaded more than 2 cm beyond the tip of the needle; (b) the amount of 5% lidocaine in 7.5% dextrose be limited to 100 mg in establishing the initial block; (c) less concentrated local anesthetic be used; and (d) the total dose of drug administered be limited in a manner consistent with the duration of the operation.

Normally, 5% lidocaine solution for spinal anesthesia is given by single injection and doses greater than 100 mg are rarely used. However, with a spinal catheter, there is a temptation to inject more 5% lidocaine solution when spinal anesthesia is inadequate. We speculate that spinal anesthesia doses of 5% lidocaine in 7.5% dextrose exceeding 200 mg may cause cauda equina syndrome.

A possible mechanism for these neurologic deficits is maldistribution of 5% lidocaine in 7.5% dextrose. In

fact, we commented on this problem in our earlier report concerning continuous spinal anesthesia with a microcatheter (1). We suggested that nonuniform distribution of the local anesthetic was due to a slow flow rate as the local anesthetic leaves the catheter tip owing to high resistance to injection when microcatheters are used. We further suggested that when inadequate anesthesia occurs, a solution of different density be used and the patient's position be altered to "direct" the local anesthetic to the poorly blocked nerves.

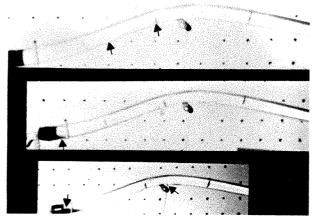
In this report, we present pictures produced with a spinal canal model to demonstrate how neural damage might occur with continuous spinal anesthesia. The hypothesis is based on the fact that nerves exposed to large volumes of 5% lidocaine solution may be damaged (2,3). Apparently, all deficits reported to the Kendall Company involve the cauda equina. Nerves in the cauda equina are devoid of protective sheaths as they pass through the distal end of the dural sac, and neural damage may occur when they are exposed to large volumes of hyperbaric 5% lidocaine solutions. This is analogous to the neural toxicity that can occur if large volumes of chloroprocaine containing sodium bisulfite intended for epidural anesthesia are injected into the cerebrospinal fluid (CSF) (4).

The spinal canal model we used consists of venous tubing used during open heart operations cut to the length of the dural sac and filled with lactated Ringer's solution (specific gravity [SG] = 1.005), which has essentially the same SG (1.006) as CSF. (All specific gravities in this study were measured using an American Optical TS Meter at 20°C.) Injections can be made to mimic spinal anesthesia. Local anesthetics are colored with methylene blue dye to aid in visualizing the distribution of the local anesthetic in the model.

Figure 1 shows the injection of 1 mL (50 mg) of 5% lidocaine in 7.5% dextrose through a Kendall Cospan 28-gauge catheter inserted at the peak of the lumbar

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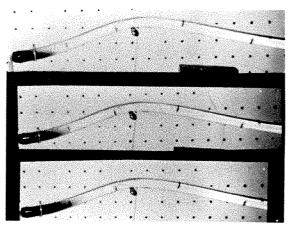
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<u>Figure 1</u>. The distribution of 1 mL (50 mg) of 5% lidocaine in 7.5% dextrose when injected through a 28-gauge catheter into a model of the subarachnoid space. (The model is in the supine horizontal position.) The catheter enters the model as seen in the lower panel (right arrowhead) and extends to the left for 3 cm (the catheter is not visible inside the model). The upper and middle photographs were taken during injection of the lidocaine. The lower photograph, taken immediately after injection, shows the dye clearly pooled at the distal end of the tube (*left arrowhead*). (See text for further details.)

lordosis and directed caudally a distance of 3 cm. Injection was made with a 1-mL tuberculin Luer lock syringe with the spinal model in the supine horizontal position. The stream of local anesthetic was visible to the observers during the injection but is not detectable in the photographs. However, the stream (localized to the area between the arrowheads shown in the upper panel of Figure 1) flowed distally and rolled along the lower portion of the spinal curve to pool in the sacral end of the model (middle panel, arrowhead). Immediately after injection, the dye was clearly pooled at the distal end of the tube (lower panel, arrowhead). Figure 2 shows the effect of injecting additional 1-mL (50 mg) volumes of 5% lidocaine in 7.5% dextrose. As shown in Figure 2, the total amount of 5% lidocaine solution injected into the model is as follows: upper panel, 2 mL (100 mg); middle panel, 3 mL (150 mg); lower panel, 4 mL (200 mg). The time that elapsed between these additional injections was approximately 5–10 min.

Accumulation of large volumes of 5% lidocaine in 7.5% dextrose, as shown in the model (Figure 2), may prove to be neurotoxic to the cauda equina nerves as they pass through the pooled local anesthetic en route to their destination. The small amount of 5% lidocaine solution normally used for single-injection spinal anesthesia does not produce neurotoxicity because it is rapidly diluted out by the CSF into which it is injected; and it is further decreased in concentration by vascular absorption, uptake into nervous tissue, and diffusion across the dura into the epidural space. However, during continuous spinal anesthe-



<u>Figure 2</u>. Photographs taken immediately after injection showing the effect of injecting additional 1-mL volumes of 5% lidocaine in 7.5% dextrose after injection of 1 mL of 5% lidocaine (Figure 1). (See text for further details).

sia, it is possible to inject volumes of 5% lidocaine solution so great that they displace the CSF, thus preventing their dilution by CSF. Although a large volume of 5% lidocaine in 7.5% dextrose may displace CSF and prevent its dilution, this does not mean that the concentration of lidocaine shown in the figures can ever increase and exceed 5%.

Figure 3 shows an alternative approach to injection of local anesthetic solutions during continuous spinal anesthesia. The upper panel shows the injection of 2% plain lidocaine (1 mL, 20 mg). This solution, though reported to be isobaric (5), is in fact slightly hyperbaric (SG = 1.014) but much less so than 5% lidocaine in 7.5% dextrose (SG > 1.035). The 2% plain lidocaine solution distributes itself more uniformly than the heavier 5% lidocaine in 7.5% dextrose. The middle panel shows the injection of an additional 1 mL of 2% plain lidocaine solution (total volume now 2 mL). At this point, the model contains only 40 mg of lidocaine but the distribution appears equivalent to that which occurred with 3-4 mL of 5% lidocaine in 7.5% dextrose (Figure 2). In the event that 40 mg (2 mL) of 2% lidocaine solution injected in this way does not produce adequate anesthesia, we suggest injecting a hypobaric solution, for example, 1 mL of 0.375% bupivacaine made hypobaric by addition of an equal volume of distilled water to 0.75% plain bupivacaine. This solution is clearly hypobaric (SG = 1.004), as shown in the lower panel of Figure 3. Figure 4 upper panel shows the injection of an additional milliliter of 0.375% hypobaric bupivacaine solution. Now the spinal canal (in the supine horizontal position) is nearly uniformly filled with local anesthetic from the peak of the lumbar lordosis distally. Yet, the amounts of local anesthetic are only 40 mg of lidocaine and 7.5 mg of bupivacaine. The photograph in the lower panel of Figure 4, taken 5

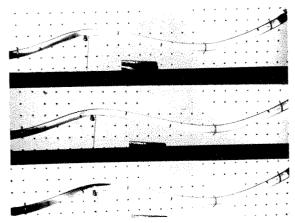


Figure 3. Spinal canal model (see text for details) showing alternative approach to injecting local anesthetic solutions during continuous spinal anesthesia when inadequate spinal anesthesia occurs. *Upper panel*, immediately after injection of 1 mL of 2% plain lidocaine (20 mg). *Middle panel*, approximately 2 min after injection of another milliliter of 2% lidocaine (40 mg total). *Lower panel*, immediately after injection of 1 mL of hypobaric 0.375% bupivacaine (3.75 mg).

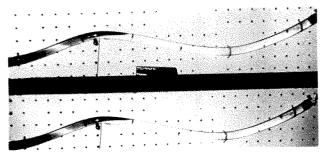


Figure 4. Spinal canal model showing the effect of injecting an additional 1 mL of hypobaric 0.375% bupivacaine (7.5 mg total). Lower panel, same as upper panel but 5 min after injection. The spinal canal is nearly uniformly filled with local anesthetic from the peak of the lumbar lordosis and distally.

min after the second bupivacaine injection, shows that the solutions remain fixed because of their density and the shape of the model.

Should the level of anesthesia at this time still not be sufficient, the patient can be repositioned for a short period of time to direct the hypobaric bupivacaine solution in a cephalad direction (Figure 5). After the solution has achieved the desired level, repositioning in the supine horizontal position prevents further spread of the hypobaric solution (Figure 5, middle and lower panels).

We would like to emphasize that the validity of this model is based on an assumption that is not entirely valid. What happens to the concentration and localization of local anesthetics injected into the model does not accurately represent what happens in vivo in patients because the model assumes that there is no change in concentration of local anesthetic after

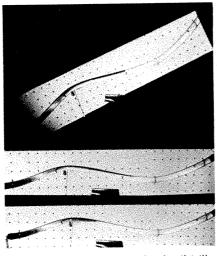


Figure 5. Spinal canal model (see text for details) illustrating the effect of position on the distribution of hypobaric bupivacaine. *Upper panel*, head-up posture for 30 s. *Middle panel*, further spread in the cephalad direction is prevented by returning the model to the supine horizontal position. *Lower panel*, 2 min after returning the model to the supine horizontal position, the hypobaric bupivacaine has migrated back toward the peak of the lumbar lordosis.

injection. This is, of course, not correct, as the concentration and the amount of local anesthetic in the CSF after injection decrease rapidly for three reasons: (a) uptake into neural tissue, (b) vascular absorption, and (c) diffusion from the CSF through the dura into the epidural space. However, this loss of local anesthetic under clinical conditions after injection into the subarachnoid space does not necessarily invalidate the use of the model as used in this report.

We hope these figures provide anesthesiologists with appreciation of the distribution of local anesthetics within the spinal subarachnoid space when continuous spinal anesthesia is given. Using low-concentration solutions of lidocaine and bupivacaine may prevent the development of cauda equina syndrome.

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Morbidity From Paraspinal Depo Corticosteroid Injections for Analgesia: Cushing's Syndrome and Adrenal Suppression

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Key Words: HORMONES, ADRENAL—steroids. COMPLICATIONS, CUSHING'S SYNDROME FROM DEPO STEROIDS.

Chronic back pain is a common problem. Paraspinal ligament, intrafacet joint, and epidural injection of depo preparations of corticosteroids are often administered to provide relief. The side effects of corticosteroids are well known and include Cushing's syndrome and adrenal suppression. Reports have been published of adrenal suppression with Cushing's syndrome after both intraarticular and intramuscular corticosteroid injections (1,2). However, neither Cushing's syndrome nor clinically significant adrenal suppression has been reported after intrafacet, paraspinal, or epidural corticosteroid injections (3). This report documents Cushing's syndrome in three patients after parenteral injection of long-acting corticosteroids for management of chronic pain.

Case Reports

Patient 1

A 44-yr-old woman with chronic low back pain and a past history of laminectomy and L4-5 hemidiscectomy in 1984 was admitted to the Orthopedic Clinic at The Mary Imogene Bassett Hospital for treatment. Under fluoroscopic guidance, bilateral L4-5 and L5, S1 facet joints were injected in June 1987 with a total of 150 mg of triamcinolone acetonide. The patient had marked relief until December 1987 when the procedure and dosing were repeated.

In January 1988, the patient was referred to our Endocrine Clinic for evaluation of her facial swelling,

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which began after the second injection. Physical examination was significant for moon facies. Her serum chemistries were normal, and morning plasma cortisol concentration ($<1.0 \mu g/dL$) was undetectable. As undetectable levels of plasma cortisol suggest adrenal insufficiency, an adrenocorticotrophic hormone (ACTH)-stimulation test was performed. Cortrosyn (α 1–24 corticotropin, 0.25 mg) was given as a single intravenous injection. Plasma cortisol concentrations were measured at 0, 30, and 60 min. The cortisol response was markedly subnormal (Table 1). One hypothesis for explaining the dichotomy of Cushing's syndrome and the suppressed adrenal response is persistence of triamcinolone in the plasma. Elective L4-5, S1 fusion was delayed until February 1988 when adrenal response to ACTH had become normal and cushingoid features had resolved. The patient tolerated the operation without corticosteroid coverage.

Patient 2

A 64-yr-old woman was admitted to the General Medical Clinic at The Mary Imogene Bassett Hospital in January 1988 for evaluation of facial swelling. In October 1987, the patient received a total of 150 mg of triamcinolone acetonide injected, under fluoroscopic guidance, into the intraspinous ligament at T9-11 for hypertrophic arthritis. The treatment was repeated in November 1987 because of exacerbation of pain. The patient's symptoms and signs of fatigue, weakness, nausea, hypertension, moon facies, truncal obesity, and skin thinning developed after the second treatment in November and progressed until the time of her evaluation in January 1988. Her serum chemistries and thyroid hormone concentrations were normal. An ACTH-stimulation test was performed because of suspicion of iatrogenic Cushing's syndrome with concomitant adrenal suppression. The results (Table 1) were confirmatory. Again, the dichotomy of Cushing's syndrome with suppressed adrenal func-

Table 1. Laboratory Data

		Plasma		a cortisol ACTH	Urinary
Patient	Date	cortisol (µg/dL)	Time (min)	Amount (μg/dL)	cortisol (µg/24 h)
1	1/88	<1.0	0	1.1	
		(undetectable)			
			30	8.3	
			60	10.9	
	2/88		0	2.6	
			30	23.6	
			60	25.9	
2	1/88		0	1.0	
			30	6.2	
			60	9.2	
	3/88				60 ^b
	7/88		0	6.9	
			30	34.1	
			60	34.9	
3	3/87	<3	0	3.0	12°
			30	4.0	
			60	5.0	
	5/87				<20
	6/87	3			33
	9/87				22
	6/88	22.			30

^{*}Normal plasma cortisol response to ACTH: baseline, >5 µg/dL; delta, >7 μg/dL; and maximum, >20 μg/dL. Normal (75-270 μg/dL). Normal (20-90 μg/dL).

tion suggested persistent plasma concentrations of triamcinolone. In March 1988, a 24-h urine test showed low levels of free cortisol (Table 1), indicating persistent adrenal suppression. In July 1988, 7 mo after corticosteroid injection, the signs and symptoms of Cushing's syndrome had resolved and adrenal response to ACTH had returned to normal.

Patient 3

A 25-yr-old man underwent C5-6 and C6-7 partial hemilaminectomies and C5-6 left foraminotomy at the University of Virginia Health Sciences Center in November 1986 for chronic neck and left arm pains. The patient received eight cervical paraspinal and one cervical epidural injection of methylprednisolone acetate within 3 mo, with the last injection in March 1987. The paraspinal injections consisted of five separate doses of 20 mg and one each of 16, 30, and 60 mg. The total dose was 286 mg; dosing intervals ranged from 2 to 14 days, with the majority between 7 to 10 days. In March 1987, the patient was noted to be markedly cushingoid with central obesity, moon facies, and violaceous abdominal striae. On random

testing, plasma cortisol (Table 1) was undetectable. An ACTH-stimulation test was markedly subnormal. The 24-h urinary levels of free cortisol (12 μ g/24 h) were subnormal. The patient was followed up regularly in the Endocrine Clinic for iatrogenic adrenal suppression with concomitant Cushing's syndrome. As documented by a normal 24-h urine level for free cortisol, the patient's hypothalamic-pituitary-adrenal (HPA) axis recovered by June 1987, 3 mo after diagnosis. However, at 20 mo, the moon facies, central obesity, and violaceous striae persisted.

Discussion

This is, to the best of our knowledge, the first report of Cushing's syndrome with adrenal suppression after intrafacet joint, paraspinous ligament, and epidural injections of depo preparations of corticosteroids. These treatments resulted in clinically significant and prolonged morbidity in patients 2 and 3, as well as surgical delay in patient 1.

Pharmacologic doses of exogenous corticosteroids suppress the HPA axis by inhibiting ACTH secretion. With prolonged exposure to pharmacologic plasma concentrations, the stigmata of Cushing's syndrome develop. However, as in patient 1, significant adrenal suppression may develop without obvious signs and symptoms of Cushing's syndrome. Similar findings have been reported after single-dose intraarticular and multiple intramuscular injections of methylprednisolone acetate, triamcinolone acetonide, and dexamethasone acetate. A single intraarticular injection of 40 mg of methylprednisolone acetate into a knee suppressed plasma cortisol levels for 1 wk (4). A single injection of 40 mg of triamcinolone acetonide and multiple intramuscular injections totaling 56 mg of dexamethasone acetate suppressed plasma cortisol levels for approximately 4 wk (2,5). The recognition of adrenal suppression is especially important in the preoperative patient, in whom the stress of anesthesia and operation may precipitate adrenal crisis.

The commonly administered depo preparations for intrafacet, paraspinal, and epidural injection include triamcinolone diacetate and acetonide and methylprednisolone acetate. Discussions about the above procedures emphasize individual preference for therapeutic regimens; however, reported doses of corticosteroids have been 10 mg of methylprednisolone acetate per facet for intrafacet treatments and 80–120 mg of methylprednisolone acetate or 80 mg of triamcinolone diacetate each week for epidural injections (6–9). Triamcinolone acetonide, used in patients 1 and 2, is the least water-soluble and, therefore,

possesses the longest duration of antiinflammatory effect and greatest suppression of the HPA axis (3). Other than total dose, important variables known to affect the duration of HPA suppression include dosing interval and number of injection sites. Adrenal suppression has developed in patients receiving intramuscular triamcinolone acetonide either every 2 or 4 wk; this did not occur in patients receiving injections every 6 wk (10). In studies of methylprednisolone acetate, 40 mg injected into two knees produced higher levels of plasma prednisolone than 80 mg injected into a single joint (4). In all patients, the total dose and number of injection sites contributed to development of Cushing's syndrome and adrenal suppression, although in patient 3 the dosing interval was also an important factor.

In summary, clinicians must be aware of potential complications from intrafacet joint, intraspinous ligament, and epidural injection of depo corticosteroids. Even though the information discussed above is based on studies of intramuscular and large-joint injections, knowledge of these studies allows development of a reasonable strategy to minimize morbidity. Because of sustained action, triamcinolone acetonide is the preferred preparation for chronic pain. However, because of inhibition of HPA function and the morbidity of Cushing's syndrome, each treatment should be restricted to the smallest number of involved joints with the lowest possible dose. Moreover, a dosing interval of every 6 wk decreases the risk of adrenal suppression. Finally, one must be alert to possible adrenal suppression, particularly if a

surgical procedure is anticipated. Adrenal crisis may follow if adequate perioperative glucocorticoids are not administered.

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Ultrasound-Guided Cannulation of the Internal Jugular Vein. A Prospective, Randomized Study

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Key Words: VEINS, INTERNAL JUGULAR—cannulation. ANATOMY, INTERNAL JUGULAR VEIN—cannulation.

The right internal jugular vein (RIJ) is a commonly used route for access to the central circulation because of its accessibility during surgery, direct route into the right atrium, and predictable location. The standard approach to RIJ cannulation uses visual and palpable anatomic landmarks to guide needle placement and is associated with a 95% success rate (1). Cannulation of the RIJ carries the potential for serious complications from unintentional puncture of surrounding structures (1-3). Ultrasound imaging, by providing visualization of the RIJ and surrounding structures, may facilitate RIJ location and decrease the incidence of complications. This study compares the ease, safety, and success rate of RIJ cannulation using a standard approach based on anatomic landmarks alone with an ultrasound-guided approach.

Methods

With approval by the University of Pennsylvania Institutional Review Board, 160 cardiothoracic surgical patients needing RIJ cannulation were prospectively studied. The patients were randomly assigned to cannulation with anatomic landmarks alone (control group) or with ultrasound guidance (ultrasound group). The level of clinical experience of the person performing the cannulation was recorded, as was the presence or absence of good anatomic landmarks. Good landmarks included palpable division of the

sternocleidomastoid muscle and a palpable carotid artery pulse.

The ultrasound device used a 7.5-MHz transducer (SiteRite, Dymax Corp., Pittsburgh, Pa.) or a 5.0-MHz transducer (Sonos 500, Hewlett-Packard, Andover, Mass.), covered by a sterile sheath, and a two-dimensional image display. The image allowed identification of the carotid artery and the RIJ by their relative position, compressibility of the vein (Figure 1), expansion of the vein on performing the Valsalva maneuver (Figure 2), and visible pulsation of the artery.

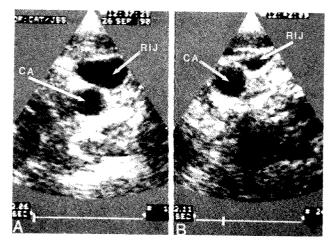
In all patients intradermal 1% lidocaine provided local anesthesia. In the control group, the lidocaine injection was made at the apex of the angle formed by the division of the sternocleidomastoid muscle. Then, with the patient in a 15°-30° Trendelenburg position, an 18-gauge × 6.35-cm-long radiopaque catheter over a 20-gauge introducer needle was inserted through the local anesthetic wheal at a 45° angle directed toward the ipsilateral nipple. In patients in the ultrasound group, the ultrasound probe was positioned under sterile conditions at the level of the thyroid cartilage and the RIJ was identified. The site of local anesthetic injection and the placement and direction of the cannulating needle were determined with the aid of the ultrasound image. In both groups, the number of needle advances from the subcutaneous tissue required before entering the RIJ was recorded.

The time between injection of local anesthetic and entry into the RIJ was recorded. Central venous cannulation was confirmed in all patients by connecting the catheter to a pressure transducer, observing the waveform, and measuring the pressure (1). Unintentional arterial punctures were recorded.

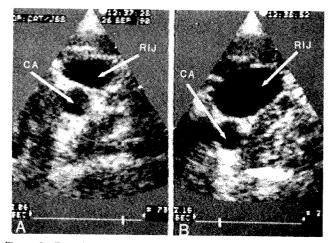
The two groups were compared for the number of needle advances required by the Mann-Whitney test, and for the time required for cannulation by Student's *t*-test. The χ^2 test was used to compare the incidence of arterial puncture and success on the first pass. Statistical significance was defined as P < 0.05.

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<u>Figure 1</u>. Two-dimensional ultrasound images of the RIJ and carotid artery (CA). The marked decrease in RIJ diameter with external compression is demonstrated: (A) before compression, (B) during compression.



<u>Figure 2</u>. Two-dimensional ultrasound images of the RIJ and carotid artery (CA). The marked increase in RIJ diameter upon performing the Valsalva maneuver is demonstrated: (A) before Valsalva, (B) during Valsalva.

Results

The two groups were similar with respect to age, height, weight, presence of good anatomic landmarks, and clinical experience. Cannulation of the RIJ was successful in all 77 patients in the ultrasound group and in 80 of 83 patients (96%) in the control group. In the three patients not cannulated in the control group, cannulation was judged a failure in one patient after the 15th attempt and in two patients after arterial puncture occurred during the 6th and 10th attempt, respectively.

Patients with ultrasound guidance required an average \pm sD of 1.4 \pm 0.7 needle advances (range, 1–4), whereas in the control patients an average of 2.8

Table 1. Results

	Control $(n = 83)$	Ultrasound $(n = 77)$
Ultimately successful cannulations	80 (96%)	77 (100%)
Successful first attempt cannulations ^a Attempts per cannulation	45 (54%)	56 (73%)
$Mean \pm sp^b$	2.8 ± 3.0	1.4 ± 0.7
Range	1-15	1-4
Time per cannulation (s)		
Mean ± sp ^c	117 ± 136	61 ± 46
Range	8-400	15-180
Arterial punctures	7 (8.43%)	1 (1.39%)

 $^{^{}a}P \le 0.05, \ \chi^{2} \text{ test.}$

 \pm 3.0 advances (range, 1–15) were required for cannulation (P < 0.05). Fifty-six of 77 (73%) patients in the ultrasound group were cannulated with one attempt as compared with 45 of 83 (54%) in the control patients (P < 0.05). Average time required was 61 \pm 46 (range, 15–180 s) in the ultrasound group and 117 \pm 136 s (range, 8–400 s) in the control group (P < 0.05). There were seven carotid punctures in the control group (8.43%) and one in the ultrasound group (1.39%) (P = 0.09, χ^2 ; P = 0.04 before Yates' correction) (Table 1).

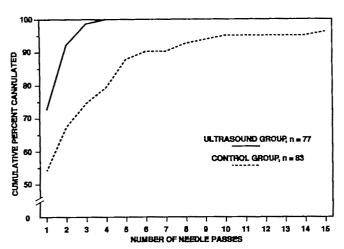
Discussion

In the present study cannulation of the RIJ was facilitated by ultrasound guidance. In the control group 96% of patients were successfully cannulated. This result is comparable to that reported previously from this institution for a similar patient population. Use of ultrasound guidance in the present study increased the success rate from 96% to 100% and the proportion of patients cannulated on the first attempt from 54% in the control group, similar to the 43.3%reported by Goldfarb and Lebrec (4), to 73%. Although both increases were statistically significant, were they clinically important? Two of the three patients judged cannulation failures in the control group had successful cannulation of the RIJ with a single attempt using ultrasound guidance. This suggests that cannulation failure would be extremely rare if ultrasound guidance was used regularly. In addition, the need for more than one attempt, especially the occasions when multiple attempts (defined as >4) were necessary, would be equally rare. The attending anesthesiologist for the third patient elected to obtain central venous access by cannulation of the external jugular vein.

 $[^]bP < 0.05$, Mann–Whitney test.

P < 0.05, Student's *t*-test.

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<u>Figure 3</u>. Cumulative percent of patients successfully cannulated versus the number of attempts required for cannulation (with and without ultrasound guidance).

Figure 3 compares the cumulative percent of patients successfully cannulated versus the number of attempts for the two groups. In the ultrasound group, all patients were cannulated with four or fewer attempts. For the eight control patients not cannulated after six attempts, the success rate was 25% or less per subsequent attempt. This is in agreement with an earlier report that cannulation is unlikely after the sixth attempt (4). A study of 29 critically ill patients, evaluating use of ultrasound for urgent RIJ cannulation by intensivists, reported a 65% successful cannulation rate in 17 control patients, which increased to 100% in the 12 ultrasound patients (5). In that smaller study all six failures after five attempts were successfully cannulated with ultrasound guidance. The much higher failure rate in that study compared with the present study (35% vs 4%) may be explained by our more controlled circumstances of elective surgical patients in the operating room versus urgent cannulation in critically ill patients in the intensive care unit. Unfortunately that study did not report the success rate on first attempt.

The incidence of arterial puncture of 8.43% in the control group is consistent with the previously reported incidence of 2%–16% (1,6). Arterial puncture occurred in only one patient in the ultrasound group. In this patient, ultrasound imaging demonstrated that the RIJ was directly anterior to the carotid artery at the level of the apex of the sternocleidomastoid muscle, instead of the usual position lateral to the carotid artery. As the cannulating needle was slowly advanced, the carotid artery was unintentionally punctured, as evidenced by bright red blood and brisk pulsatile flow. The anatomic information provided by the ultrasound image indicated that the

catheter passed through the vein and punctured the carotid artery. As the catheter was slowly withdrawn, continuous aspiration revealed bright red blood, a cessation of blood flow, and then darker colored blood. The catheter was advanced into this vessel. Subsequent to that occurrence, RIJ position directly anterior to the carotid artery was observed in two additional patients imaged with ultrasound. Successful cannulation without arterial puncture was achieved at a site more caudad to the level of the apex of the division of the sternocleidomastoid muscle where ultrasound imaging demonstrated that the RIJ was positioned lateral rather than anterior to the artery. When this anatomy is encountered, scanning the neck for a more optimal orientation of the two vessels is recommended. If the RIJ is directly anterior to the artery along its entire course in the neck, an extremely low and laterally angled meticulous needle advancement, while avoiding compression of the vein, may prevent arterial puncture.

Direct visualization of the RIJ with two-dimensional imaging revealed the ease with which the RIJ can be compressed with minimal external pressure. Even without external pressure, the vein can be compressed by the cannulating needle during advancement before vessel entry. This may account for the often observed phenomenon of blood aspiration while withdrawing the needle rather than during advancement.

Doppler ultrasound has also been used for localization of the internal jugular vein (7,8). This technique is dependent on differentiating arterial and venous sounds and does not provide imaging for localizing the internal jugular vein. Only one of these studies used a control group, and there a 77.3% success rate in the Doppler group at first attempt compares favorably with 73% in our ultrasound group and is much better than the 28.6% in their control group. Although the low velocity venous flow in the RIJ produces a distinctly different sound from the characteristic pulsatile sound of blood flow in the carotid artery, visualization of the structures with ultrasound permits more distinct separation of vein and artery.

The time saved with ultrasound-guided cannulation is not readily apparent if average times are compared. For patients successfully cannulated without ultrasound, time required for cannulation ranged from 8 to 400 s with 11 of 80 (14%) patients requiring at least 5 min. This does not include the three patients in whom cannulation could not be accomplished. They required 5, 8, and 10 min before the cannulation attempt was aborted. Two of these patients had successful RIJ cannulation with ultrasound guidance,

requiring one needle advance and less than 1 min of additional time. All patients in the ultrasound group were cannulated in 3 min or less (range, 15–180 s).

In this era of cost containment the issue of cost must be addressed. Institutions using echocardiography to monitor patients already have available the necessary equipment. In other institutions the decrease in unsuccessful cannulations, patient discomfort, and time required for cannulation as well as the avoidance of complications, some of which are lethal, further argue for ultrasound guidance.

It is concluded that two-dimensional ultrasound-guided cannulation of the internal jugular vein facilitates locating the RIJ, permitting safe entry with fewer attempts, in less time, and decreases the incidence of arterial puncture. Additionally, some patients who cannot be cannulated using anatomic landmarks alone, may be successfully cannulated with ultrasound guidance.

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Neuromuscular Response to Succinylcholine-Vecuronium Sequence in Three Myasthenic Patients Undergoing Thymectomy

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Key Words: COMPLICATIONS, MYASTHENIA GRAVIS. NEUROMUSCULAR RELAXANTS, SUCCINYLCHOLINE, VECURONIUM.

The basic defect in myasthenia gravis is a decrease in the number of functional acetylcholine receptors at the postsynaptic neuromuscular junction. This decrease is due to inactivation or destruction of the receptors by circulating antiacetylcholine receptor antibodies. It is estimated that 70%–80% of previously functional receptors are lost (1). This may explain the resistance to depolarizing muscle relaxants such as succinylcholine (2–4) and the marked sensitivity to nondepolarizing muscle relaxants such as vecuronium (5–7).

The present report investigates the neuromuscular effects of succinylcholine-vecuronium sequence in three myasthenic patients undergoing thymectomy.

Methods

Investigation was carried out in three myasthenic patients undergoing thymectomy through a median sternotomy. The three patients suffered from generalized myasthenia gravis (Osserman grades 2A and 2B) (8), which was adequately controlled by therapy. They had no preoperative risk factor predicting the need for postoperative respiratory support (9). Anticholinesterase medications were discontinued the evening before the operation in the first two patients and were continued until the morning of the operation in the third patient. Patient data are presented in Table 1.

Before induction of anesthesia, a blood sample was taken for measurement of plasma cholinesterase levels (10) from one of the two patients whose anticholinesterase medications were discontinued the evening before the operation and from the third patient whose medications were continued until the morning of the operation.

Neuromuscular transmission was monitored by electromyography (Datex, Instrumentarium Corp., Helsinki, Finland). The ulnar nerve was stimulated supramaximally at the wrist every 20 s, and the resulting electromyographic response was displayed. The monitor uses the train-of-four principle at a stimulation rate of 2 Hz and features an automatic search for the supramaximal stimulus. The monitor computes the ratio of the fourth to the first evoked response (T_4/T_1 ratio).

The three patients were premedicated intramuscularly with 0.6 mg of atropine and 5 mg of oral diazepam. Anesthesia was then induced with 5 mg/kg of thiopental. After induction of anesthesia and while the patients were breathing 100% oxygen, the electromyographic response was recorded until a steady response was achieved. Succinylcholine (1.5 mg/kg) was then injected intravenously and its neuromuscular effect monitored. When maximal neuromuscular blockade was achieved, the trachea was intubated. Anesthesia was then maintained with 70% nitrous oxide in oxygen supplemented by 2–3 μ g/kg of fentanyl. After recovery from succinylcholine blockade, incremental doses of 0.01 mg/kg of vecuronium were injected to achieve 95% depression of the T_4/T_1 ratio.

In the three patients, neuromuscular monitoring was continued throughout the surgical procedure, and intermittent doses of 0.01 mg/kg of vecuronium were injected whenever a T_4/T_1 ratio of 25% was observed. At the termination of the operation, residual neuromuscular block was reversed in the first two patients by a mixture of 0.05 mg/kg of neostigmine and 0.02 mg/kg of atropine and was allowed to

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Table 1. Patient Data

Sex	Age (yr)	Weight (kg)	Severity (Osserman classification)	Duration of myasthenia (mo)	Thymus	Current anticholinesterase medications (mg/day)	Other therapy
F	30	82	2B	6	Normal	Pyridostigmine, 360 Neostigmine, 90	Prednisone, 50 mg daily
F	46	59	2 A	6	Thymoma	Pyridostigmine, 360 Neostigmine, 90	
F	21	50	2A	10	Normal	Pyridostigmine, 480	Prednisone, 50 mg daily Plasmapheresis



Figure 1. Electromyographic tracing in the first patient, showing the effect of 1.5 mg/kg of succinylcholine. Maximal depolarizing neuromuscular block was achieved after 40 s.



<u>Figure 2</u>. Electromyographic tracing in the first patient, showing the effect of 0.01 mg/kg of vecuronium. A 95% depression of the T_4/T_1 ratio, corresponding to a 60% depression of T_1 /control, was achieved after 5 min.

recover spontaneously without reversal in the third patient.

Results

In these three myasthenic patients, 1.5 mg/kg of succinylcholine resulted in initial muscle fasciculations followed by complete neuromuscular block within 60 s, and the trachea could be easily intubated. The block was depolarizing in nature, as evidenced by a T_4/T_1 ratio that ranged between 0.80 and 1.0. Recovery of neuromuscular transmission reached T_1 height of 75% after 10–15 min (Figure 1).

The plasma cholinesterase level in the patient whose anticholinesterase medication was discontinued the evening of the operation was 1.47 U/mL and

<u>Table 2</u>. Initial Vecuronium Doses Required to Achieve 95% Depression of the T_4/T_1 Ratio and Total Vecuronium Doses Required to Maintain a T_4/T_1 Ratio <25% Throughout Operation

Patient No.	Initial blocking dose (mg/kg)	Total dose (mg/kg)	Duration of operation (min)
1	0.01	0.06	. 130
2	0.01	0.08	145
3	0.02	0.07	135

the dibucaine number was 90. In the patient whose medication was continued until the morning of the operation, cholinesterase activity was 1.08 U/mL (normal value in our population 2.5–6 U/mL) and the dibucaine number was 90.

After recovery from succinylcholine block, 0.01 mg/kg of vecuronium produced 95% depression of the T_4/T_1 ratio in the first two patients (Figure 2), whereas two incremental doses of the same amount were required to achieve the same degree of block in the third patient. The total dose of vecuronium required to maintain a T_4/T_1 ratio less than 25% throughout the operation amounted to 0.06 mg/kg in the first patient, 0.08 mg/kg in the second patient, and 0.07 mg/kg in the third patient (Table 2).

At the termination of the operation, the residual vecuronium blockade was completely reversed in the first two patients by 0.02 mg/kg of atropine and 0.05 mg/kg of neostigmine, as evidenced by a T_4/T_1 ratio above 0.90. In the third patient, spontaneous recovery after the last increment of vecuronium was achieved without reversal after 25 min. The trachea was extubated in the operating room when the patients were awake, cooperative, and breathing adequately. On the evening of the operation, the three patients resumed their oral anticholinesterase medication.

Discussion

It has been generally recommended that use of muscle relaxants be avoided in myasthenic patients who may demonstrate abnormal neuromuscular responses to both depolarizing and nondepolarizing relaxants (11,12).

Myasthenic patients may show resistance to succinylcholine (2–4). Phase II block may also develop early, with slow recovery (3,12). In the present report, 1.5 mg/kg of succinylcholine was administered to facilitate tracheal intubation. In all three patients, succinylcholine rapidly produced depolarizing neuromuscular block and provided excellent intubating conditions within 60 s. Recovery from succinylcholine block was observed after 10–15 min. The results suggest that resistance of the myasthenic patients to succinylcholine may be evident only when small doses are used but may not be encountered with high doses (3). The dose of succinylcholine we used represents 3–5 times the ED₉₅ in normal subjects and 1.25–2.0 times the ED₉₅ in myasthenic patients (4).

The use of preoperative anticholinesterase medications in myasthenic patients may inhibit the plasma cholinesterase activity (10) and thus delay the hydrolysis of succinylcholine (13). However, our report shows that the plasma cholinesterase activity was only moderately decreased irrespective of whether the anticholinesterase medications (14) were discontinued the evening of operation or were continued until the morning; hence, recovery from succinylcholine was not prolonged in any of the three patients.

After recovery from succinylcholine blockade, the nondepolarizing neuromuscular relaxant vecuronium was administered. The present report confirms previous investigations that demonstrate sensitivity to vecuronium in the myasthenic patient (5–7). In our myasthenic patients, 95% depression of the T_4/T_1 ratio could be achieved by 0.01-0.02 mg/kg of vecuronium, which is approximately 10%-20% of the blocking dose in normal patients. The marked sensitivity to vecuronium observed in our myasthenic patients might have been exaggerated by the prior administration of the depolarizing relaxant succinylcholine, which may desensitize the cholinergic endplate receptors (15) and hence may potentiate the nondepolarizing blockade of subsequently administered vecuronium. Also, the sensitivity to vecuronium in myasthenic patients may be exaggerated by the discontinuation of their anticholinesterase therapy. However, the dose of vecuronium required in the first two patients whose medications were discontinued the evening before the operation was not different from that required in the third patient whose medications were continued until the morning of the operation; the small number of cases cannot, however, be used to determine statistical significance of our findings.

Despite the increased sensitivity of myasthenic patients to nondepolarizing relaxants, both vecuronium (5–7) and atracurium (16,17) are rapidly eliminated; hence, their administration can be easily adjusted to achieve an appropriate neuromuscular blockade that can be completely reversed or even recover spontaneously at the termination of the surgical procedure.

In conclusion, a succinylcholine-vecuronium sequence can be safely used in myasthenic patients, provided neuromuscular transmission is adequately monitored. The technique may be particularly advantageous when rapid sequence induction of anesthesia is indicated in the myasthenic patient (4). Succinylcholine can rapidly provide excellent intubating conditions, and the subsequent administration of vecuronium can be carefully adjusted to maintain the required degree of neuromuscular blockade.

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Effect of Preinduction Glycopyrrolate on the Hemodynamic Response to Anesthesia With Propofol

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Key Words: ANALGESICS, FENTANYL. ANESTHETICS, INTRAVENOUS—proposol. PARASYMPATHETIC NERVOUS SYSTEM, GLYCOPYRROLATE.

Induction of anesthesia with propofol is often followed by a reduction in blood pressure that can sometimes be substantial with minimum blood pressure values recorded within 2 min of induction (1). This decrease in blood pressure is due to an increase in venous capacitance (2) and possibly also to a reduction in arteriolar tone (3,4). The decrease is usually greatest in the first few minutes after induction when surgical stimulation has not commenced and when only small quantities of intravenous fluids have been given. Several authors have attempted to reduce this hypotension with a variety of strategies including manual or computer-controlled infusion schemes (5,6) and infusion induction at lower pump speeds (7).

When glycopyrrolate or atropine was given 5 min before induction and maintenance of anesthesia with propofol and alfentanil, a similar increase in heart rate was seen but, unlike atropine, glycopyrrolate reduced the decrease in systolic and diastolic blood pressures at 3, 6, and 9 min after induction (8). This difference between the effects of atropine and glycopyrrolate was attributed to differences in affinity of atropine and glycopyrrolate for the M₁ and M₂ muscarinic receptor subtypes. As this antihypotensive effect of glycopyrrolate appeared to be independent of heart rate, we considered that there might be a different dose-response relationship to that for tachycardia. Other examples of this are well known.

Droperidol, for example, is an antiemetic at a low dose and a major tranquilizer at a higher dose. In addition, as the study population of Skues et al. (8) was small, we have retested the original hypothesis by including control patients who did not receive glycopyrrolate.

Skues et al. recorded the lowest blood pressures at 3 and 6 min and were unable to demonstrate any benefit from glycopyrrolate 9 min after induction. We have therefore limited our study to the first 5 min of anesthesia to avoid the confounding hemodynamic influences of laryngoscopy and surgery while covering the times at which propofol-induced hypotension is usually most profound (2). We have investigated the effects of three different doses of glycopyrrolate on the hemodynamic consequences of induction and early-maintenance anesthesia with propofol.

Methods

The study was approved by the South Manchester District Ethical Committee, and all patients gave informed consent in writing. Healthy female patients (n=99) of ASA physical status I or II, weighing 45–115 kg and aged 18–64 yr who were scheduled for elective breast or gynecologic surgery, were recruited into the study. Outpatients received no premedication; patients expected to stay overnight received 10–20 mg of oral temazepam 100 min preoperatively.

An anesthetist, who was not otherwise involved in the study, mixed glycopyrrolate injection and 0.9% saline solution to give a solution containing 0, 200, 400, or 600 μ g of glycopyrrolate in 8 mL. Five minutes before the start of induction, 0.1 mL/kg of this solution was administered intravenously in a randomized double-blind manner giving a glycopyrrolate dose of 0, 2.5, 5, or 7.5 μ g/kg. After 4 min, 1 μ g/kg of intravenous fentanyl was given; and 1 min later, anesthesia was induced by infusing propofol at 1200 mL/h using an Ohmeda 9000 (B.O.C. Healthcare, U.K.) electronic syringe pump in bolus mode while the patient counted aloud.

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Table 1. Demographic Data and Induction Dose for the Four Treatment Groups

	Group 1 (control)	Group 2	Group 3	Group 4
Glycopyrrolate dose (μg/kg)	0	2.5	5	7.5
n	23	25	25	25
Age (yr)	41.0 ± 2.3	38.4 ± 2.8	38.8 ± 2.3	38.9 ± 2.9
Weight (kg)	63.6 ± 2.1	60.8 ± 1.8	64.3 ± 2.3	65.9 ± 3.2
Propofol (mg/kg)	2.3 ± 0.1	2.3 ± 0.1	2.3 ± 0.1	2.2 ± 0.1

There were no significant differences between the groups. Data are mean \pm sem.

Induction of anesthesia was considered to be completed at cessation of counting, and the pump speed was then reduced to deliver propofol at 10 mg·kg $^{-1}$ ·h $^{-1}$. After induction, patients breathed 100% oxygen through a Mapleson A anesthetic breathing system and a face mask. Apnea lasting more than 30 s was treated by gentle manual inflation of the lungs. Six minutes after induction, the study was terminated. Anesthesia was continued with agents and techniques appropriate to the scheduled surgical procedure. Arterial blood pressure was measured at 7, 6, 4, and 1 min before induction and 2 and 5 min after the start of induction, using an automatic sphygmomanometer calibrated in accordance with the manufacturer's instructions. Electrocardiogram (lead CM₅) was monitored throughout the study. Demographic data were compared using the Kruskal-Wallis test. Analysis of variance (Scheffé F-test) was used to evaluate between-group differences in heart rate and blood pressure.

Results

There were no differences in age, weight, and induction dose of propofol between the four groups (Table 1). (Groups 1–4 received 0 [control], 2.5, 5, and 7.5 μ g/kg glycopyrrolate, respectively.) Only 24 patients were recruited to the saline (control) group (group 1) as one randomization envelope was inadvertently used for a male patient in another study. One patient from the control group vomited during induction of anesthesia with anesthesia immediately discontinued and the operation postponed; data from this patient have been excluded from our analysis.

Heart rate and blood pressure were similar in groups 1–4 before administration of glycopyrrolate/saline solution (P > 0.05). Heart rate was increased by glycopyrrolate (P < 0.001), with significantly greater increases resulting from the larger doses (Table 2). After induction, systolic, mean, and diastolic blood pressures decreased significantly (P < 0.001) in all

four groups, with patients in groups 2–4 showing a decrease similar to that in the control group (Table 2). There was no relationship between the glycopyrrolate dose and the subsequent decrease in blood pressure on induction. No arrythmias or ST segment changes were detected in any patient.

Discussion

Although propofol caused a substantial reduction in blood pressure within 2 min of induction, we were unable to demonstrate any hemodynamic benefit from pretreatment with glycopyrrolate in our study population. Our range of glycopyrrolate treatments spanned the therapeutic range of the drug, and its antivagal effect is clearly demonstrated by the doserelated increases in heart rate seen in the different groups. Even if groups 2–4 were combined for comparison against the control group, the only blood pressure measurement to differ significantly would be systolic blood pressure at 2 min after induction with an 8 mm Hg difference between the treated and untreated groups (P < 0.05, Scheffé F-test). This difference, however, is too small to be clinically significant. To be clinically worthwhile, we believe that the difference in blood pressure between the treated and untreated groups should be at least 10%, if not more. Our study had a power of 80% to detect an 11 mm Hg difference in mean arterial pressure between groups with P < 0.05, and we conclude that if glycopyrrolate does have any effect on the hypotension seen at the start of propofol anesthesia, it is too small to be useful and that alternative antihypotensive measures such as fluid loading and careful dose titration are more appropri-

Glycopyrrolate caused a significant tachycardia in patients in groups 2–4 (Table 1), yet this did not prevent nor even attenuate the hypotension caused by propofol. If, as suggested by Goodchild and Serrao (2), the hypotensive effect of propofol is due to an increase in venous capacitance, then inducing

Table 2. Heart Rates and Systolic, Mean, and Diastolic Blood Pressures of Groups 1-4 After Propofol Inductiona

	Min after				
	induction	Group 1	Group 2	Group 3	Group 4
Glycopyrrolate dose μg/kg		0	2.5	5	7.5
n		23	25	25	25
Heart rate	-7	75.3 ± 3	79.6 ± 2.2	78 ± 2.9	81.6 ± 3.1
	-6	77.3 ± 3	79.8 ± 2.6	78.8 ± 2.7	82.7 ± 2.7
	-4	74.3 ± 3.2	84.7 ± 2.6	88.9 ± 4	101.5 ± 4.3
	-1	74.5 ± 2.9	86.3 ± 2.6	97.5 ± 4.4	114.2 ± 4.1
	2	72.7 ± 2	80.4 ± 2.1	95.2 ± 3.1	101 ± 3
	2 5	69.8 ± 2	73 ± 2.2	89.3 ± 3.1	95.3 ± 2.7
Systolic	-7	123.1 ± 3.6	121.8 ± 4.4	123.3 ± 3.9	130 ± 3.7
,	-6	120.7 ± 3.5	121.3 ± 4.3	120.2 ± 3.5	130.7 ± 4.4
	-4	118.6 ± 3.3	122.8 ± 3.8	122.6 ± 3.9	132.2 ± 3.5
	-1	119.2 ± 3.6	122.8 ± 3.7	121.4 ± 3.6	132.7 ± 3.7
	2 5	93.3 ± 2.5	99.2 ± 3.4	101.2 ± 3.4	105.4 ± 2.9
	5	93.1 ± 2.5	95.8 ± 3.1	99.2 ± 3.1	100.2 ± 2.2
Mean	-7	95.2 ± 2.8	92.8 ± 3.7	93.1 ± 3	98.8 ± 2.9
	-6	93.7 ± 2.5	92.3 ± 3.6	93.2 ± 2.9	99.8 ± 3.2
	-4	92.3 ± 2.1	93.6 ± 3.3	93.4 ± 2.8	100.7 ± 2.4
	-1	92 ± 2.7	93.4 ± 2.9	93.4 ± 2.6	101.2 ± 2.9
		70 ± 2.1	71.5 ± 2.9	73.8 ± 2.8	76.3 ± 2.4
	2 5	68.2 ± 1.8	68.6 ± 2.7	72.8 ± 2.3	76.6 ± 1.8
Diastolic	-7	76 ± 2.3	74.4 ± 2.8	74.2 ± 2.2	78.2 ± 2
	-6	75.7 ± 2.3	72.7 ± 2.5	73.5 ± 2.1	78.6 ± 2.3
	-4	74 ± 1.5	76 ± 3.1	75 ± 2.2	82.2 ± 1.7
	-1	74 ± 2.1	75.5 ± 2.3	76.3 ± 1.9	81.7 ± 1.9
	2	57.8 ± 1.8	57.8 ± 2.5	61 ± 2.5	61.8 ± 2.3
	5	55.8 ± 1.7	55.6 ± 2.5	59.8 ± 2	61.7 ± 1.5

^{*}Glycopyrrolate or placebo was given at -5 min, 1 μ g/kg of fentanyl at -1 min, and propofol at 0 min. There were no significant differences between the groups. Data are mean \pm sem.

tachycardia may not compensate hypotension caused by inadequate cardiac preload. Measures that increase preload such as fluid loading or elevation of the legs may be more effective. Our patients received 1 μ g/kg of fentanyl before induction of anesthesia. We do not consider that this small dose influenced the hemodynamic effect of propofol.

Skues et al. (8) speculated that the selective antagonism by glycopyrrolate of muscarinic receptor subtype M_2 may account for the blood pressure sparing effect that they described. If this interpretation is correct, then other selective M_2 antagonists could perhaps be investigated in a similar manner, although our results suggest that little benefit is likely in fit patients. Further work is in progress to evaluate this use of glycopyrrolate in the elderly and in patients of ASA physical status III or IV.

To summarize, 99 female patients of ASA physical status I or II scheduled for elective breast or gynecologic surgery were given 0, 2.5, 5, or 7.5 μ g/kg of glycopyrrolate in a randomized double-blind manner 5 min before induction of anesthesia with 1 μ g/kg of fentanyl and propofol (average dose, 2.3 \pm 0.1 mg/kg) followed by maintenance of anesthesia with a propofol infusion at 10 mg·kg⁻¹·h⁻¹.

Although glycopyrrolate significantly increased heart rate in a dose-related manner, the decrease in blood pressure 2 and 5 min after induction was similar in all groups. In view of the dose-related increase in heart rate caused by glycopyrrolate and in the absence of data to support its use, we do not consider giving glycopyrrolate before induction of anesthesia to be an effective stratagem to reduce the hypotension induced by propofol.

We thank Professor T. E. Healy for his encouragement.

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High-Frequency Jet Ventilation in the Anesthetic Management of a Patient With Tracheoesophageal Fistula Complicating Carcinoma of the Esophagus

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Key Words: VENTILATION, HIGH FREQUENCY. SURGERY, ESOPHAGEAL—tracheoesophageal fistula. COMPLICATIONS, FISTULA—tracheoesophageal.

Carcinoma of the esophagus is the fifth most common cause of cancer deaths in male adults in Hong Kong (1). Surgical treatment includes radical resection or palliative bypass (2). Anesthesia for esophageal operation is always a challenge. Poor nutrition and hypoproteinemia are usually associated with dysphagia and malignant cachexia. Most patients are elderly. Many are also smokers with impaired pulmonary function. Tracheoesophageal fistula (TEF) may further complicate esophageal carcinoma. Palliative bypass procedures are indicated in such patients to restore the ability to swallow (3) and to prevent pulmonary soiling by diverting oral intake and secretions away from the fistula. This is a report on high-frequency jet ventilation (HFJV) used during esophageal bypass operation to allow adequate ventilation without gas leakage through a TEF.

Case Report

A 69-yr-old Chinese man, a chronic smoker with chronic obstructive pulmonary disease, was admitted to our center for treatment of esophageal carcinoma and chest infection. Endoscopy showed an ulcerated obstructive esophageal carcinoma 28 cm from the upper incisors. Gastrografin (meglumine diatrizoate) swallow demonstrated a TEF at the carina. Aspiration of contrast occurred during the Gastrografin study.

Bronchoscopy showed a widened carina with tumor erosion of the tracheal mucosa and compression of the left main bronchus. Total parenteral nutrition was instituted before palliative esophageal bypass operation. The pulmonary complications were treated by chest physiotherapy, antibiotics, and salbutamol inhalation.

Preoperative assessment showed an emaciated ASA physical status III male patient weighing 54 kg. Laboratory findings included the following: hemoglobin, 11 g/dL; serum albumin, 3.7 g/dL; forced vital capacity, 3.2 L; forced expiratory volume at 1 s, 2.16 L; peak expiratory flow rate, 260 L/min. Arterial blood gas analysis (ABG) while the patient was breathing room air showed a pH of 7.43, an arterial partial pressure of oxygen (Pao₂) of 97 mm Hg, and an arterial partial pressure of carbon dioxide (Paco₂) of 39 mm Hg. Other laboratory data were within normal limits. Chest roentgenogram showed right lower lobe consolidation and bilateral basal pneumonia.

The patient was premedicated intramuscularly with 50 mg of meperidine and 0.4 mg of atropine 1 h before operation. Before induction of anesthesia, a 16F nasogastric tube was inserted successfully past the tumor, bypassing the esophageal opening of the TEF, into the stomach for continuous drainage and suction. After preoxygenation, general anesthesia was induced intravenously with 75 μ g of fentanyl and 200 mg of thiopental. After assuring satisfactory chest expansion through gentle manual mask ventilation with 100% oxygen, 75 mg of succinylcholine was given intravenously. The trachea was sprayed with 10% lidocaine, and a Mallinckrodt Hi-Lo Jet Tube (ETT) (Mallinckrodt Critical Care, Glens Falls, N.Y.) with a 9.0-mm internal diameter was inserted. The tip of the ETT was placed just above the carina. Gentle manual ventilation with isoflurane in oxygen

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Table 1. Respiratory and Hemodynamic Data During High-Frequency Jet Ventilation

Variables	Time (min)						
	0	30	60	90	120	150	180
HFJV settings							
Fio ₂	1.00	0.35	0.35	0.35	0.35	0.35	0.35
Resp rate/min	200	150	150	150	150	150	150
IT%	30	40	40	4 0	40	40	40
DP (bar)	2.5	1.5	1.5	1.6	1.6	1.8	1.7
EEP (cm H ₂ O)	2.0	1.0	1.0	2.0	1.0	1.0	1.0
TV (mL)	108	104	108	106	106	119	113
PIP (cm H ₂ O)	15	15	14	15	15	15	17
Respiratory data							
Sao ₂ (%)	100	100	100	100	100	100	100
Pao ₂ (mm Hg)	517.5	238.5	234.0	231.8	217.5	201.8	187.5
ETCO ₂ (%)	6.2	4.7	4.8	4.5	5.3	5.0	6.2
Perco ₂ (mm Hg)	47.1	35.7	36.5	34.2	40.3	38.0	47.1
Paco ₂ (mm Hg)	51.0	36.8	42.0	40.5	43.5	38.3	48.0
Hemodynamic data							
MAP (mm Hg)	114	102	111	93	80	98	107
HR/min	64	61	63	60	58	54	71

HFJV, high-frequency jet ventilation; Fio₂, inspiratory fraction of oxygen; resp rate, respiratory rate; IT, inspiratory phase of respiratory cycle; DP, driving pressure; EEP, end-expiratory pressure; TV, tidal volume; PIP, peak inspiratory pressure; Sao₂, arterial saturation with oxygen; Pao₂, arterial partial pressure of oxygen; ETco₂, end-tidal carbon dioxide; PErco₂, partial pressure of ETco₂; Paco₂, arterial partial pressure of carbon dioxide; MAP, mean arterial pressure; HR. heart rate.

The respiratory and hemodynamic values were normal during HFJV; ABG analysis was performed every 30 min for correlation.

through a Bain system resulted in a gas leak through the TEF with gas escaping from the nasogastric tube.

High-frequency jet ventilation was then instituted using an Acutronic AMS 1000 Universal Jet Ventilator (Acutronic Medical Systems, Jona-Rapperswil, Switzerland) with the following initial settings (Table 1): inspiratory fraction of oxygen (Fio₂), 1.0; respiratory rate, 200/min; inspiratory phase of respiratory cycle, 30%. The driving pressure was adjusted to 2.5 bar so that the delivered tidal volume was 108 mL. Peak inspiratory pressure and the end-expiratory pressure were 15 and 2 cm H₂O, respectively (Table 1). Isoflurane (1%) in oxygen was given at a rate of 6 L/min through the Bain system for entrainment by the HFJV stream. After demonstrating the absence of gastric distention and gas leakage from the nasogastric tube, the 100% oxygen to both HFJV and Bain systems was replaced by a mixture of 65% nitrous oxide and 35% oxygen. There was no change in oxygenation after the introduction of nitrous oxide.

Anesthesia was maintained with isoflurane, nitrous oxide, and intravenous fentanyl supplement. Muscular relaxation was maintained with intravenous infusion of atracurium. An Engström Eliza Duo Carbon Dioxide Analyser (Gambro Engström, Bromma, Sweden) was used for monitoring end-tidal carbon dioxide (ETCo₂) at 5 min-intervals by intermittent interruption of HFJV and by deep manual breaths.

Samples for ABG measurements were taken every 30 min at a time when ETco₂ measurements were also made. Other monitoring included continuous intraarterial blood pressure, electrocardiogram, and pulse oximetry (Sao₂). The hemodynamic and respiratory parameters remained normal throughout the procedure (Table 1). A retrosternal Kirshner bypass operation was performed, with the stomach mobilized and anastomosed to the cervical esophagus through an artificial retrosternal tunnel. The upper esophageal stump was closed and the lower esophagus was connected to a jejunal loop through an end-to-side anastomosis. Operating conditions were very satisfactory. At the end of the operation, residual muscular relaxation was reversed with intravenous neostigmine and atropine, and the trachea was extubated. The patient, breathing 40% oxygen, was taken to the intensive care unit. Postoperative recovery was smooth. The patient was discharged from the intensive care unit and was tolerating a soft diet by the 10th postoperative day. He was discharged 4 wk after the operation.

Discussion

The anesthetic management of patients with TEF complicating carcinoma of esophagus for palliative

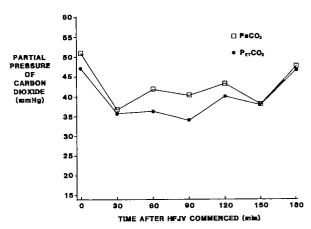
bypass operation is associated with several problems (4). First, repeated pulmonary aspiration occurs preoperatively resulting in bronchopneumonia. Second, during controlled ventilation, the anesthetic gas mixture leaks through the TEF leading to inadequate lung inflation, hypoxemia, and carbon dioxide retention. The stomach may become distended by the inflating gas through the TEF during positive pressure ventilation (IPPV), which may increase the leakage of gastric contents through the fistula and cause further pulmonary soiling. Third, as the operation is palliative, the TEF and its associated preoperative risk factors are still present in the postoperative period. It is important that the patient breathes spontaneously after operation because conventional IPPV is difficult (5).

Palliative bypass operation of the type done in this patient is a long procedure (220 min) and requires muscular relaxation. Spontaneous respiration during operation therefore is impossible. It has been reported that IPPV to the left lung could be carried out after successful isolation of the TEF by insertion of either a double-lumen endobronchial tube (4) or a single-lumen ETT under guidance of a flexible fiberoptic laryngoscope (5). However, these techniques were not applicable in this patient because, first, one-lung ventilation is well known to be associated with hypoxemia (6,7) especially in patients with preoperative chest complications. Second, the carinal mucosa was eroded by tumor. Endobronchial intubation or instrumentation might have caused hemorrhage from the tumor with subsequent pulmonary soiling. The same may occur with endobronchial jet catheters.

Consequently, we decided to intubate the trachea with the ETT tip situated above the tumor and the TEF opening so that HFJV could be used. This technique gave adequate ventilation with a much smaller tidal volume and lower mean airway pressure than IPPV so that the gas leak through the TEF was minimized (8–10). These were well demonstrated by the maintenance of normal ABG data, Sao₂, and ETco₂, and the absence of gastric distention.

The initial HFJV settings were empirical, resulting in a tidal volume of 2 mL/kg (11). Settings were titrated against the Sao₂ and ETco₂. Initially, 100% oxygen was given and anesthesia was maintained by isoflurane and intravenous fentanyl. In the absence of gastric distention, nitrous oxide was used to reduce the requirement for other anesthetics.

High-frequency jet ventilation is associated with the entrainment of an unknown volume of gas. In our patient, this was complicated by the possible gas loss through the TEF. Ventilation also varied during sur-



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Figure 1. The Paco₂ correlated well with partial pressure of ETco₂ (Perco₂) measured by deep breath maneuver during temporary interruption of HFJV.

gical manipulation, especially when the retrosternal tunnel was created. Adequate ventilation can only be sustained in situations such as this case by adjustment of HFJV settings according to measured oxygenation and CO₂ elimination (12).

The pulse oximeter provides noninvasive *continuous* and reliable information on arterial oxygenation. However, information on CO₂ level cannot be obtained by *continuous* ETco₂ during HFJV because the frequency response of most capnographs is too slow and because extensive mixing of expiratory and inspiratory gases occurs during HFJV. Animal experiments have shown, however, that ETco₂ readings recorded after one to three deep breaths during interruption of HFJV correlate well with Paco₂ (8,13). The findings in our patient confirm this in humans (Figure 1 and Table 1).

In conclusion, HFJV is a valuable technique in patients with TEF in which fistula isolation is impossible. Continuous Sao₂ and intermittent deep breath ETco₂ measurements are adequate for assessing ventilation and for adjusting HFJV settings.

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Letters to the Editor

A Hairy Problem

Key Words: INTUBATION, TRACHEAL.

To the Editor:

Difficulty with tracheal intubation can jeopardize patient safety. A thorough preoperative evaluation will usually identify most potential problems, thus allowing the laryngoscopist to take special precautions to facilitate the procedure. We recently encountered an unusual cause of difficult tracheal intubation.

A 43-yr-old, 75-kg Sikh man from India was admitted for repair of a left scapholunate dislocation. Past medical history and physical examination were unremarkable. There was no family history of anesthetic complications. In the operating room a left axillary block was performed, but the block was inadequate; it was therefore decided to proceed with general anesthesia. After preoxygenation, anesthesia was induced with 250 mg intravenous thiopental followed by 120 mg intravenous succinylcholine. Ventilation was easily accomplished by mask. On attempted laryngoscopy the patient's jaw was not relaxed. Trismus after succinylcholine was considered. A nerve stimulator demonstrated loss of twitch. A Macintosh 3 laryngoscope blade was passed into the pharynx with great difficulty due to a very restricted mouth opening. Several attempts at



<u>Figure 1</u>. After successful tracheal intubation, examination of patient revealed a tight strap under his beard that had severely limited our ability to open his mouth despite complete muscle relaxation.

visualizing the larynx were unsuccessful. Only the epiglottis could be seen. Tracheal intubation was finally achieved "blindly."

After intubation, further examination of the airway revealed the cause of the problem. Because of his religious beliefs, the patient had not cut his hair and had woven his locks together and tied them tightly with a strap under his jaw (Figure 1). This prevented us from being able to open his mouth fully despite complete muscle relaxation.

Certain anatomic features are associated with intubation difficulties and should be sought preoperatively (1-3). Often, the planned operation, the patient's disease, or a history of trauma to the head and neck will alert the anesthesiologist to potential problems with endotracheal intubation. The difficulty we encountered was completely unanticipated. It was only after intubation was successfully accomplished that the true cause was discovered. Because our patient had appeared on cursory preoperative examination to have a normal anatomy, no further investigation of his airway had been performed. Had his airway been thoroughly evaluated, the limited ability to open his mouth would have been discovered.

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The Tape Sign

Key Words: ANESTHESIA, REGIONAL—rectal. SURGERY, ANORECTAL.

To the Editor.

I am a colon and rectal surgeon who performs many of my anorectal procedures with the patient in the jack-knife

prone position under regional anesthesia. On completion of the anesthetic block and after the patient has been placed in the operating position, adhesive tape straps are applied to retract the patient's buttocks. The anesthesiologist may then check the progress of the block by direct needle prick or by similar local stimulation. This is, however, most often unnecessary. Before draping the patient, I perform a digital rectal examination noting motor and sensory loss that is indicative of the degree of anesthesia achieved. Sigmoidoscopy is then done after which the patient is draped for the procedure. At this time, the buttock strapping, which was initially quite taut, will, if the block is satisfactory, invariably become somewhat wrinkled and/or loose, requiring replacement of the tape at the sides of the operating table. Although not universally reliable, this "tape sign" derived from increasing muscle relaxation (and perhaps to a lesser extent, from diminution of the patient's anxiety when he finds he is not able to feel pain or other local stimuli) will suggest to the surgeon and the anesthesiologist that the block was successful. This phenomenon has been observed on numerous occasions. I wish to share this clinical information with any interested colleagues.

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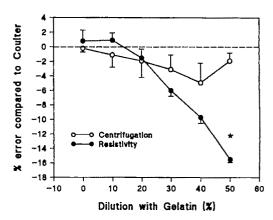
Colloids and Hematocrit Measurement by Conductivity

Key Words: BLOOD, HEMATOCRIT—measurement.

To the Editor:

We read with interest the study by McMahon and Carpenter comparing conductivity-based hematocrit determination with conventional laboratory methods in autologous blood transfusion (1). We used the same three devices in 10 healthy patients to determine whether centrifugation (minicentrifuge Compur 1100, Bayer) or resistivity (Stat Crit, Fumouze) were reliable methods of hematocrit determination, compared with a reference method (Coulter counter model S+2) (2), when blood samples were diluted either with dextran (Plasmacair, Cernep Synthelabo) or with gelatin (Plasmion, Roger Bellon) from 10% up to 50%.

Our results were quite similar. With dextran, whatever the method used, the hematocrit was underestimated but no more than 5% (NS). The same result was observed with gelatin when the hematocrit was measured by centrifugation. Conversely, when samples were diluted with gelatin and the hematocrit was estimated by resistivity, the underestimation increased with the dilution reaching 15.5% (P < 0.05) with 50% dilution (Figure 1). The addition of gelatin (which are small proteins electrically loaded) to blood increases the blood's conductivity and gives falsely low readings when hematocrit is determined by resistivity. Our



<u>Figure 1</u>. Error of hematocrit determination by centrifugation or by resistivity compared with Coulter method when blood samples are diluted by gelatin (mean \pm sem, $\star P < 0.05$).

results suggest that hematocrit determination by resistivity should be avoided in patients receiving gelatin.

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Clinical and Radiologic Evidence of Epidural Dorsomedian Ligamentous Strands

Key Words: ANATOMY, EPIDURAL SPACE—dorsal midline strands. ANESTHETIC TECHNIQUES, EPIDURAL—dorsal midline strands.

To the Editor:

I read with interest the case report by Gallart et al. (1). I would like to offer a comment. In Figure 1 it appears that some of the radiologic contrast used to outline the catheter has escaped into the subdural space on the right side extending to the pedicle of T-10. In Figure 2, some of the air and the radiologic contrast that was injected has probably crossed the midline. The dural cuff of T-12 can be seen on the right. Figure 3 is consistent with radiologic contrast in the subdural space on the right and in the epidural space on the left. The figures are typical for a patient who has had epiduroarachnoiditis (2).

It would be interesting to know if the patient had a previous epidural injection, myelography, radiation therapy, or other procedure that might have produced fibrotic changes in the epidural space. It is my understanding that the plica mediana dorsalis should not be conceived as a septum but as a dorsomedian dural fold (3). The fold is formed as the dura is prevented from collapsing by fibrous strands going from the ligamentum flavum to the medial portion of the dura. I submit that, ordinarily, these fibrous strands (dorsomedian ligamentous strands) do not form a septum dividing the epidural space into right and left side. However, after an inflammatory process, the spread of drug in the epidural space can be impeded and the dura can become adherent to the ligamentum flavum (4).

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In Response:

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We thank Dr. Rocco for his interest in our article (1). Although our Figure 1 could be diagnosed as a subdural blockade, that is not the case in Figure 2. As the subdural space is a very narrow one, its x-ray image is formed by very thin lines at both sides and by a weak radiologic image in the center (2). However, this is not the image in Figure 2 in which the contrast material escaping through the intervertebral foramina can be seen. Moreover, the clinical course was not that of a subdural block (3), and although this can be asymmetric, to our knowledge, it has not been reported as a cause of unilateral analgesia (1). An explanation that could satisfy Dr. Rocco and us would be that the catheter being a multiorifice one (Perifix Portex), the tip was in the subdural space and the other orifices were in the epidural space.

If the contrast material had crossed the midline, as Figure 2 suggests, it could have been through the anterior epidural space (1). We agree that fibrotic changes in the epidural space after inflammation, operation, or other procedures can cause unilateral analgesia (1) but these were excluded in our case. As some studies report, plica mediana dorsalis can really act as a barrier and can impede the diffusion of contrast material (1). Local anesthetics can spread more easily in the epidural space, but this structure

could make it difficult, thus causing a unilateral epidural blockade. That is what we obtained.

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Unusual Cause of Endotracheal Tube Obstruction

Key Words: EQUIPMENT, TUBES endotracheal obstruction. COMPLICATIONS, TRACHEAL TUBES—obstruction.

To the Editor:

Small-sized endotracheal tubes (ETTs) are prone to partial or complete obstruction with potentially harmful consequences. Most anesthesiologists have encountered cases of ETT obstruction owing to secretions, blood clots, foreign bodies, position-induced kinking, herniated cuffs, or manufacturing defects. I report here a somewhat unusual cause of iatrogenic ETT obstruction.

A 3-wk-old, 3-kg infant was scheduled for repair of bilateral inguinal hernias. His previous medical history was unremarkable except for mild prematurity. General anesthesia was induced by face mask with $O_2/N_2O/halothane$. After injection of 0.3 mg of vecuronium, the trachea was intubated orally under direct vision with a No. 3.0 ETT. Correct position of the ETT was confirmed by auscultation and by observing a normal capnographic tracing. A 10F suction catheter was then inserted through the nose to decompress the stomach, which had become somewhat distended during ventilation with the face mask.

Suctioning, however, did not relieve the gastric distention, and an attempt was made to reposition the suction catheter. The catheter, however, could not be pulled out of the nose; at the same time, it became impossible to ventilate the patient and the end-tidal CO₂ curve disappeared. Immediate laryngoscopy showed the suction catheter tightly knotted around the ETT completely obstructing it. The suction catheter was cut, the ETT was removed, and

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the trachea was reintubated with another No. 3.0 ETT. The operation then proceeded without further complications.

This case of iatrogenic ETT obstruction did not result in any harmful consequences owing to the early recognition of the problem and immediate access to the airway allowing a rapid reintubation. Had the airway been less readily accessible, the result could have been far less benign.

The insertion of a suction catheter (e.g., nasogastric tube, esophageal stethoscope, temperature probe) in the mouth or nose of an intubated patient can potentially either dislodge or obstruct the ETT. This is more likely to happen with the small ETT used in infants and children. If the catheter does not slide easily into the esophagus, the probability of curling and, as in this case, knotting increases. When resistance is encountered during this maneuver, it is best to withdraw the catheter and try a different approach.

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Isoflurane and Outcome After Coronary Artery Surgery

Key Words: ANESTHESIA, CARDIAC—outcome. ANESTHETICS, VOLATILE—enflurane, isoflurane. SURGERY, CARDIOVASCULAR—coronary artery bypass grafting.

To the Editor:

Inoue et al. (1) recently reported the results of a study on cardiac surgical patients suggesting a significantly greater incidence of postoperative myocardial infarction and inhospital deaths when the patients were given isoflurane than when given enflurane. Uncontrolled anesthetic protocol, nonstandardized treatment of myocardial ischemia, unreporting of hemodynamic parameters, and failure to report the incidence of myocardial ischemia before and during the operation are just a few of many criticisms that can be made in challenging the results and conclusions of this report. Despite their reassurances of similar demographics between the patients receiving enflurane versus isoflurane, the authors' failure to randomize resulted in two groups of patients that appear to us to be different. The increased requirement for antihypertensive drugs, the difference in use of catecholamines and/or inotropic drugs, and the differing need for intraaortic balloon pump use after cardiopulmonary bypass cannot, we believe, be explained simply by which volatile anesthetic the patients received. Perhaps if the authors had reported on the number of patients with left main coronary artery stenosis

>90% or on the incidence of preoperative congestive heart failure, important predictors of outcome after coronary artery bypass grafting (CABG) (2), the differences between groups might have been apparent.

We urge readers to examine more closely controlled investigations before judging the suitability of isoflurane for CABG. Our group has recently reported results (3) of the myocardial effects of isoflurane and halothane in patients with steal-prone coronary anatomy undergoing CABG. Unlike Inoue et al., (1) who treated hypotension (guidelines were left to the discretion of the individual anesthesiologist) by "lightening the anesthetic level and by fluid administration and/or head-down position" for example, in the study by Pulley et al. (3) hemodynamic status was strictly controlled. There was no significant difference in the incidence of myocardial ischemia as detected by coronary artery lactate extraction or production, transesophageal evidence of new regional wall motion abnormalities, or ECG changes between the isoflurane and halothane groups (3). Finally, previous prospective randomized studies have demonstrated that a multitude of factors are significantly more important as determinants of outcome after CABG operation than anesthetic technique (4,5).

We believe that the report presented by Inoue et al. (1) does not provide sufficient evidence to support their conclusions that isoflurane adversely influences outcome of patients undergoing CABG.

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To the Editor:

In a nonrandomized trial of primary anesthetic agents, Inoue et al. (1) compared the outcome of CABG when performed with either enflurane or isoflurane anesthesia. Patients who received isoflurane suffered significantly higher rates of death and of postoperative myocardial infarction and had greater need for inotropic agents when they were weaned from cardiopulmonary bypass. The authors do not suggest a mechanism for the adverse effect of isoflurane but suggest, although with great tentativeness, that isoflurane may be inappropriate for CABG. The purpose of this letter is to suggest a mechanism for the high rate of adverse outcomes after isoflurane anesthesia—poor study design.

In their Discussion, Inoue et al. correctly write "Outcome depends, however, on many factors, including preoperative patient characteristics, anesthetic technique, and-very important-surgical factors. The conclusion of our study is based on the assumption that any factors other than the choice of anesthetics did not differ between the groups." Their assumption was, of course, incorrect because of their failure to include in their observations the surgical factor previously demonstrated to be the primary determinant of the outcome. In our randomized trial of primary anesthetic agents (2), the only significant predictors of postoperative myocardial infarction (PMI) by discriminant analysis were the operating surgeon's rating of the quality of distal anastomoses and vein grafts, an ischemic clamp time greater than 40 min, a new perioperative myocardial ischemia, and a history of chronic hypertension. Of these, the rating of the quality of the operation by the surgeon was the single most powerful predictor of PMI. The failure by Inoue et al. to include any of these documented predictors in their discriminant analysis could easily account erroneously for the poorer outcomes for isoflurane anesthesia. Inclusion of more patients with poor surgical ratings in the isoflurane group could by itself account for the higher incidence of all three adverse outcomes in the isoflurane group.

The authors point out that each of the seven surgeons performed approximately the same number of operations using enflurane and isoflurane, and therefore, inequality in surgical skill and judgment was eliminated as a cause of the observed differences. However, surgeons of all skills perform less than satisfactory operations because of the poor quality of the arteries and veins that constitute the coronary bypass. The surgical rating, which proved such a powerful predictor of outcome in our randomized study, was a characteristic of the patient and his disease, not of the surgeon and his skill. Most important, the surgeon rated the quality of operation before removal of the aortic crossclamp and therefore before he could know of difficulty in weaning, PMI, or death. The surgeon therefore made a prediction by his rating, and this fact gives great credence to the value of this predictor of the obvious—that a poor operation is the most important predictor of a poor out-

As Inoue et al. did not make observations on the quality of surgical repair nor even of new perioperative ischemia, their data cannot be reexamined to account for the important intraoperative factors in outcome. Readers should properly consider the differences reported in these two groups as the result of faulty study design and not of the use of either enflurane or isoflurane anesthesia.

An additional disturbing feature of this study was the investigators' failure to adhere to their scheme of weekly alternation of the primary anesthetic. What biases caused this allocation failure and how many data were derived from improperly allocated patients? At the very least, the authors could have analyzed their data both ways—all data (as was done) compared with data from properly allocated patients only (not done). Some reassurance, or lack of it, could result from this additional data analysis.

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A Method for Preventing Endotracheal Tube Cuff Overdistention Caused by Nitrous Oxide Diffusion

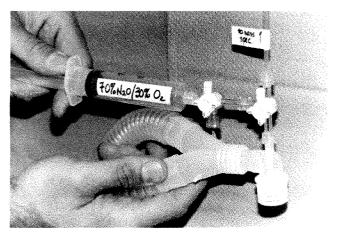
Key Words: EQUIPMENT, cuffs-endotracheal.

To the Editor:

The development of endotracheal tubes (ETTs) with high-volume, low-pressure cuffs has decreased the incidence of associated tracheal pressure injury. During general anesthesia, the use of nitrous oxide-oxygen (N_2O-O_2) mixtures can, however, defeat this safety measure, if room air is used to inflate the cuff, because N_2O diffuses into closed air spaces 34 times faster than nitrogen diffuses out, potentially resulting in ETT cuff overdistention (1,2). This is usually of minimal clinical consequence during short anesthetic procedures. During long cases, particularly those in which the anesthetist's access to the airway is limited (e.g., many ENT, neurosurgical, and plastic surgery procedures), ETT cuffs can become distended by N_2O diffusion, increasing the likelihood of significant pressure injury to the tracheal mucosa.

Raeder et al. suggested inflating the ETT cuff with anesthetic gas mixtures to reduce this problem (3). Inflation of the ETT cuff with a gas mixture containing the maximum concentration of N_2O to be used during the case (e.g., 70% N_2O , 30% O_2) will prevent further cuff distention by N_2O diffusion. We have developed a simple, more convenient

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<u>Figure 1</u>. Demonstration of syringe for cuff inflation being filled from an anesthesia circuit filled with an N_2O-O_2 mixture.

way to inflate ETT cuffs with N_2O-O_2 mixtures from the anesthesia machine circuit. The method consists simply of attaching a syringe with a three-way stopcock to a second three-way stopcock in line with the capnograph/mass spectrometer sampling port of a N_2O-O_2 primed circuit (Figure 1). Outflow from the 15-mm adaptor is occluded with a plug adaptor or finger. The N_2O-O_2 concentration in the circuit can be checked with the circuit O_2 concentration monitor and/or the mass spectrograph. The syringe can then be filled from the circuit, sealed with the three-way stopcock, and subsequently used to inflate the ETT cuff. The syringe can be conveniently filled during the preanesthetic check of the anesthesia machine and circuit.

We have used this technique in approximately a dozen suitable cases. Potential problems with the technique include loss of N_2O from the syringe should a considerable delay arise between filling the syringe and inflating the cuff. Additionally, if the patient's condition requires use of a higher Fio_2 than that in the ETT cuff, volume might be lost gradually from the cuff resulting in a cuff leak. We have experienced none of these problems in our use of cuff inflation with N_2O - O_2 thus far. As with any anesthetic technique, careful attention to proper patient selection for use of our suggested technique should minimize the incidence of problems.

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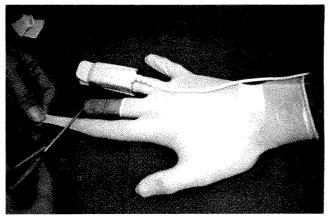
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Preventing Removal of the Intravenous Catheter in Mentally Handicapped Patients

Key Words: EQUIPMENT, CATHETERS—intravenous.

To the Editor:

Mentally handicapped patients can unwittingly be uncooperative, and after surgery, such patients often pull their intravenous catheters out. We have found that a snug-



<u>Figure 1</u>. A latex glove applied to prevent removal of an intravenous catheter by an uncooperative patient, with fingertip removed to apply a pulse oximeter.

fitting latex glove placed on the hand containing the catheter prevents this (Figure 1). After insertion of the catheter into the dorsum of the hand, a latex glove is placed on the hand. To apply a pulse oximeter to the same hand, a fingertip of the glove can be pulled, and then cut to uncover the finger. Vinyl gloves do not disrupt pulse oximetry, but they do not fit the hand snugly enough to be as useful (1).

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Anaphylactic Shock Produced by Latex

Key Words: ALLERGY, ANAPHYLAXIS—latex.

To the Editor:

Although natural rubber (latex obtained from *Hevea brasiliensis*) has been used for medical and dental treatments for many years, contact urticaria to rubber has been described only since 1979 (1). Evidence now indicates that exposure to the natural rubber of latex surgical gloves, breathing bags, or compressive bandages during anesthesia and operation can result in anaphylactic reactions (2–6).

An 8-yr-old boy, weighing 25 kg, was admitted for a right herniorrhaphy. The patient and his parents were questioned and he was considered to have no history of allergic reactions. Three surgical procedures (two for congenital glaucoma and one for left hernia) under general anesthesia had been uneventful 6, 5, and 2 yr before.

Anesthesia was induced with nitrous oxide and halothane. Caudal anesthesia was performed with a mixed solution of bupivacaine (32.5 mg) and lidocaine (130 mg). Twenty minutes after skin incision, as the last sutures were being placed, the pulse became nonpalpable. Cardiopulmonary resuscitation was initiated. Epinephrine (0.25 mg) was given intravenously. The trachea was intubated and the lungs ventilated with 100% oxygen. Airway pressures were unusually high. Chest compression could be discontinued after less than 1 min. As systolic blood pressure was only 35 mm Hg, epinephrine was given again (0.25 mg intravenously and 0.25 mg in the endotracheal tube). Hydrocortisone succinate (50 mg) and colloids (200 mL) were also administered. The child's cardiopulmonary state then appeared to stabilize. A transient generalized urticarial rash was observed. Venous blood was sampled for measurement of levels of plasma histamine, immunoglobulin E, and local anesthetics. As the child awakened, airway pressures increased and blood pressures decreased again. An epinephrine infusion (0.05 μ g·kg⁻¹·min⁻¹) was given for the next 3 h. The patient recovered uneventfully and was discharged 2 days later.

The signs observed in this case were characteristic of an anaphylactic reaction. As allergy to lidocaine and bupiv-

acaine is rare and the onset of signs was unusually delayed, the patient and his parents were questioned again. No history of allergic reactions to drugs or food could be found, but they reported several episodes of facial and periorbital swelling some minutes after he blew up rubber balloons.

Plasma levels of lidocaine and bupivacaine assayed using a gas chromatography method (respectively 3.02 and 0.53 μ g/mL) were below toxic levels. Skin prick tests were performed 6 wk later using lidocaine, bupivacaine, and a piece of washed rubber surgical glove. Only the latter proved to be positive. Plasma histamine measured by radioimmunoassay was 90.1 nmol/L (normal < 10.0 nmol/L). Latex-specific immunoglobulin E measured by radioallergosorbent testing was increased (2.8 kU/L), normal < 0.4 kU/L).

This case suggests that any preoperative assessment must systematically search for a history of rubber allergy to avoid the exposure to latex during anesthesia and operation. When in doubt, specific skin tests must be performed preoperatively.

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Book Reviews

Anesthetic Management of Difficult and Routine Pediatric Patients, 2nd ed. F. A. Berry, ed. New York: Churchill Livingstone, 1990, 457 pp, \$45.00.

This is the revised and updated presentation of pediatric anesthesia as practiced by the anesthesia group at the University of Virginia (UVA). The editor describes the goal of the book to be somewhere in between a comprehensive pediatric anesthesia textbook and a manual, and the book is just that—somewhere in between. Practicing anesthesiologists will find most aspects of modern pediatric anesthesia discussed with background information and practical application of techniques provided. Residents will be able to read this book in its entirety within a reasonable time and will emerge with a good overview of the scope and considerations of pediatric anesthesia practice.

This book is also a useful reference for the practicing pediatric anesthesiologist, as many current issues are discussed in depth and the specific practices of the UVA group are well outlined. The index is much more complete, and the new expanded form enables the reader to easily identify and locate subjects of interest. The format of the chapters is readable; and the many tables, graphs, and illustrations provide practical and current information. Three new authors join the seven contributors of the first edition, the latter having either repeated or rewritten their chapters. Most of the chapters that have been repeated in this edition have been significantly updated, and the references provided are both appropriate and current. Present controversial topics in pediatric anesthesia including alterations in NPO status and preoperative routine laboratory testing, parental presence during induction of anesthesia, early feeding, and postoperative discharge are all discussed intelligently. Especially well presented is a discussion on anesthetizing the child with an upper respiratory infection (although a subheading is entitled "UTI") including both the pros and cons in a variety of clinical situations. The use of newer pharmacologic agents in children such as cimetidine, metoclopramide, vecuronium, and atracurium is also covered but warrants a more thorough discussion than is provided. The charming introductory chapter describing the history of pediatric anesthesia has been retained essentially unchanged. The Basic Considerations chapter has been revamped and is presented as "Clinical Pharmacology of Inhalation Anesthetics, Muscle Relaxants, Vasoactive

Agents, Narcotics and Techniques of General Anesthesia," a superficial discussion of the above. An outstanding chapter on endoscopy has been added. Not only is an in-depth description of the many different types of endoscopes, lasers, and endotracheal tubes included, but an excellent discussion of clinical indications, pathology, and effects of anesthetic agents follows. A new chapter on regional anesthesia and pain control in children may be especially useful for the general anesthesiologist who is not familiar with these practices in pediatric patients.

Many chapters have new titles and have been slightly modified but remain essentially unchanged in content and illustration. Among them are the following: Physiology and Surgery of the Infant, The Difficult Airway, Acute Airway Obstruction, Epiglottitis and Croup, Asthma, Pediatric Neuroanesthesia, and Fluids and Electrolytes. On the whole, the new edition contains a great deal of worthwhile new information not only in the updated chapters but in the new titles as well. This book is a useful addition to the reference library of both pediatric and general anesthesiologists.

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Trauma: Anesthesia and Intensive Care L. M. Capan, S. M. Miller, and H. Turndoff, eds. Philadelphia: J. B. Lippincott, 1990, 884 pp, \$125.00.

Anesthesiologists encounter the enormous medical and socioeconomic burdens of trauma virtually every day that they practice in the United States. Despite this, the specialty of anesthesiology has been provided with few comprehensive textbooks on the management of trauma and its multiplicity of complications. This volume is therefore a welcome addition to the books presently available.

The text is written by multiple authors and is divided into four sections. The first section covers basic considerations of trauma and includes discussions of different aspects of resuscitation. The 12 chapters in the second section discuss the management of specific types of injury in some depth, and section three considers the complica-

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tions of trauma. The final section consists of one chapter that examines the organization of trauma services.

Overall, the print quality of this hardback volume is more than acceptable with clear text and headings that are appropriate and easy to follow. However, the print quality of a number of the algorithms and graphs, which appear to have been reproduced from a dot matrix or a daisy wheel printer, is disappointing.

In common with many publications written by several authors, this book contains some overlap between chapters. However, the overlap is usually concerning a particularly pertinent issue, such as the management of the airway in patients who have suffered trauma to the neck. However, no examples of significantly conflicting advice were noted between different chapters of the book. Capan has been a careful and competent editor to guard against this type of contradiction.

Anesthesiologists are not renowned for their holistic approach to medicine, and this reputation will remain intact because the editors did not include a chapter about the psychological aspects of trauma. The psychological sequelae of trauma can be encountered by the anesthesiologist during resuscitation or preoperative assessment in the emergency room, the ward, or the intensive care unit and also during the recovery phase when repeated anesthetics may be required.

A factual error appears on the first page. In a discussion of the historical roots of trauma management, Baron Larrey, the introducer of the "flying ambulance," is incorrectly named as Dominique Jean Lairey. The first chapter is an overview of trauma and one of its final sections describes methods of assessing injury severity. The Glasgow Coma Scale and Abbreviated Injury Scale are described, but the Trauma-Injury Severity Score, which by combining anatomic and physiologic variables probably has a higher predictive value, is only briefly mentioned. We believe that progress in the anesthetic management of trauma depends on the widespread use of a scoring system that permits comparison of outcomes.

Despite the encouraging advances in trauma care in recent years, failure of adequate airway management and of care of the injured cervical spine remain all too common causes of significant trauma-related morbidity, mortality, and litigation. The very detailed yet clear chapters on airway management and facial, neck, and cervical spine injuries were therefore a pleasure to read. These chapters appear to reinforce the salient messages that all clinicians need to learn about these important injuries.

Two other chapters deserve special mention: those on hemodynamics and on oxygen transport and uptake in trauma patients. The authors should be congratulated in making these topics easy to understand but still include the necessary theories, facts, and controversies.

Chapter 6 gives an account of transfusion therapy in trauma and includes an excellent description of the technique of autologous transfusion and the various systems available. This chapter is marred by a couple of small inaccuracies (and by some of the algorithms with poor print

quality mentioned previously). In the figure illustrating the vasomotor changes associated with transfusion, the precursor of kallikrein is incorrectly designated as kallikreinogen rather than prekallikrein. Also, the author of this chapter implies that all cases of non-A, non-B hepatitis can be referred to as hepatitis C, which is misleading.

These minor inaccuracies and omissions should not be interpreted as overall dissatisfaction. Indeed, books on the anesthesiologist's role in trauma management are rare, and the editors and authors should be congratulated on collating such a readable reference book. This book deserves a place on the bookshelves of any hospital that offers a comprehensive trauma service.

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Regional Anesthesia in Children Claude Saint-Maurice and Schulte Steinberg, eds.

Claude Saint-Maurice and Schulte Steinberg, eds. Switzerland: MediGlobe SA, 1990, 200 pp, \$70.00.

Children have long been considered unsuitable candidates for regional anesthesia because of their terror of needles. Indeed, because it is difficult to perform a nerve block in a child without the concomitant use of a general anesthetic, one can honestly ask why one should bother to perform a block at all. Furthermore, when a regional technique is utilized in an anesthetized patient there is a need for an "extra pair of hands" to support the airway and monitor the patient during the performance of a block. Finally, it is presumed that greater manual dexterity and technical excellence are required to perform nerve blocks in children compared with adults simply because of their size.

Nevertheless, the past decade has witnessed an explosion of interest and utilization of neural blockade in the clinical practice of pediatric anesthesia. Regional techniques instituted intraoperatively are used to limit the total amount of general anesthetics used, hasten arousal, minimize postoperative complications, and provide the major source of postoperative pain relief. Furthermore, unlike adult patients, children under 8 years of age receiving major conduction blocks, such as caudal or lumbar epidural anesthesia, rarely, if ever, develop hypotension.

Not surprisingly, review articles in the major anesthesia journals, refresher courses at the annual meetings, and now a monograph exclusively devoted to this issue have recently been published. This fabulously illustrated monograph is edited by Drs. Claude Saint-Maurice and Schulte Steinberg, uniquely qualified individuals who pioneered the development of regional anesthetic techniques in children, and is a testimony to their individual efforts, as well as to the efforts of our European colleagues who have been at the forefront of popularizing and investigating regional anesthesia in children.

The monograph is divided into four sections. The first is

devoted to basic principles of neural transmission, local anesthetic action, and pharmacology and describes some of the specialized equipment that may be used in performing neural blockade in children. Unfortunately, much of this equipment is unavailable in the United States. The second and largest section describes regional anesthetic techniques, with an emphasis on major conduction blockade. Unfortunately, less commonly performed blocks are either not mentioned at all (e.g., stellate ganglion block) or given very short shrift (e.g., interpleural regional blockade). Indeed, this reviewer recently had to perform a block he rarely performs, namely, an ankle block. Neither the text nor the illustrations were particularly helpful and he ended up following the advice in Moore's classic textbook, Regional Block, and placed a femoral and sciatic nerve block instead. The third and fourth sections describe the use of regional anesthesia in pain management and in special situations, such as the child with a myopathy or other neuromuscular disorders.

Unfortunately, despite the beauty of the illustrations and its remarkably low price (\$70.00), this monograph cannot be recommended to anyone other than a pediatric regional anesthesia aficionado, who will treasure it for its artwork and as a source of slides for teaching purposes. The text accompanying the illustrations is awkward, repetitious, and dull. Furthermore, the publisher's choice of text layout and fonts is exceedingly poor. Inappropriate hyphenation is particularly distracting when reading this text. Better descriptions of how to perform nerve blocks in children and of the unique features of pediatric local anesthetic pharmacology and pharmacokinetics are available in Smith's Anesthesia for Infants and Children (5th ed.) and in Gregory's Pediatric Anesthesia (2nd ed.).

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Trauma Anesthesia

John K. Stene and Christopher Grande. Baltimore: Williams & Wilkins, 1990, 510 pp, \$79.00.

The authors of this book are uniquely equipped to make the case for a separate text and subspecialty for trauma anesthesia. *Trauma Anesthesia* is more cohesive than most multiauthored texts because the majority of the authors are from one of the premier trauma centers in the United States, the Maryland Institute for Emergency Medical Service System located in Baltimore. A special challenge in writing a text in a subspecialty area is to provide enough information about a subject, e.g., airway management, that may be treated well in a standard textbook of anesthesia and at the same time expand on the uniqueness of the topic for the subspecialty. In general, most chapters strike a nice balance between background information and material that is especially apropos to trauma anesthesia.

The chapters in the book are organized in a logical sequence with introduction as to the past, present, and future of trauma anesthetic practice. They cover the main topics unique to trauma anesthesia such as problems of transport and communication, mechanisms of injury, airway management of the patient with facial and craniocervical injury, hyperbaric oxygen therapy, and medicolegal and ethical issues applicable to caring for trauma patients. Other chapters present information on the unique problems of the traumatized pregnant patient, the multiply injured pediatric patient, the patient with thoracoabdominal and orthopedic injury, the CNS-injured patient, and the burn patient. Of course shock states and resuscitation and fluid and blood therapy are presented and fully discussed. Regional anesthesia in trauma is also covered.

One of the weaker chapters is the one on temperature regulation. As hypothermia in the perioperative period is a very common complication in the trauma patient, a more in-depth discussion of the physiology and management of temperature regulation would have strengthened the book. Malignant hyperthermia should have been briefly discussed as this topic is covered in many texts in detail.

Is this book on anesthesia for trauma necessary? The reviewers say yes, because the book provides a reference text for use by anesthesiologists, certified nurse anesthetists, emergency room physicians, surgeons, and the paramedical staff working with trauma patients. The strength of this book is the practical presentations based on actual clinical experiences of the majority of the authors.

The editors are to be congratulated for putting together this book. Truly there is a "resurgence of interest in the care of trauma patients among anesthesiologists" and, thus, this book is very timely. It should find general acceptance among all anesthesiologists who manage these patients. Finally, should we consider designating trauma anesthesia a subspecialty?

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Anesthesia and Trauma. Problems in Anesthesia, Volume 4, No. 3

M. Jane Matjasko and Baekhyo Shin, eds. Philadelphia: J.B. Lippincott, 1990, 230 pp, \$30.00 for single issue.

This multiauthored book seeks to cover 10 major areas of interest in anesthesiology for trauma: the role of the anesthesiologist as a member of the trauma team, airway problems, fluid resuscitation, massive transfusion, acute spinal injuries, severe head injuries with intracranial hypertension, chest trauma, pediatric trauma, trauma and the pregnant patient, and aspects of alcohol, anesthesia, and trauma. The restricted number of pages creates a format

where concise, clearly written material of practical consequence is desirable, as opposed to in-depth reviews.

Some contributors have accomplished this task admirably. The chapter on intracranial hypertension in severe head injuries presents the pathophysiology and management of this area in a lucid fashion with complementary diagrams and more than adequate references. Pediatric anesthesia is also presented in a comprehensive and practical manner with appropriate illustrations and titles. A welcome chapter concerns pregnant patients and trauma. Background maternal physiology is presented concisely and the focus is then directed at trauma management. Areas such as the treatment of raised intracranial pressure, managment of emergency cesarean section, and discussion of anesthetic agents are covered well. The two chapters on fluid management and massive transfusion are well done. The brief outline on the mathematics of hemodilution is useful and the discussion of the crystalloid versus colloid controversy is balanced.

Two other sections missed opportunities to enlighten anesthesiologists about recent developments. The section on the anesthesiologist as a member of a trauma team might have usefully mentioned what primary and secondary evaluations are (perhaps with a flow chart) and ATLS (Advanced Trauma Life Support) certification and its value to all practitioners. Unnecessary repetition of tables detracted from this chapter and occupied space that could have been better used. The airway section was too short and concentrated unduly on iatrogenic complications of airway management. Unfortunate omissions include the new portable "litmus paper" ETCO₂ detection devices, Seldinger technique cricothyrotomy, minifiberoptic laryngoscopy for assessment of laryngeal injuries, and jet ventilation techniques.

The chapters on chest injuries and spinal injuries are adequate but do not quite fulfill their potential. Thus the spinal injury chapter omitted reference to the practical problem of anesthetic agents and their effect on somatosensory evoked potentials and neglected to discuss the sometimes considerable blood loss involved in spinal surgery. The chest injury chapter covers most important aspects, but omits discussion of the effects of IPPV on cardiac tamponade and fails to emphasize that fiberoptic bronchoscopy is advisable to assist positioning for all double-lumen tubes, not just right-sided endobronchial tubes.

In conclusion, this volume makes useful contributions in certain areas of trauma and anesthesia, most notably with respect to head injuries, pregnant patients, pediatric trauma, and aspects of fluids and transfusion. Certain other areas are not presented as well so that although this is a useful addition to anesthesia libraries, a critical focus is warranted and for some aspects of trauma and anesthesia, practitioners should read elsewhere.

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Handbook of Clinical Anesthesia P. G. Barash, B. E. Cullen, and R. K. Stoelting. Philadelphia: J. B. Lippincott, 1990, 561 pp, \$24.95.

Congratulations! A barely one pound "Baby Barash" Handbook of Clinical Anesthesia has been born. Despite the resemblance of its cover to that of the "Papa Barash" textbook, the handbook is not merely a miniaturized version of the textbook. Although based on the textbook, the handbook focuses mostly on hard, applicable data.

Of the 55 chapters of the textbook, 44 are represented in the handbook. In addition, the handbook includes a chapter on drug interactions and useful appendices on hemodynamic and respiratory formulas; an atlas of elementary electrocardiography; a list of about 120 drugs regularly used by anesthesiologists; a malignant hyperthermia protocol; the resuscitation protocols of the American Heart Association; and the ASA Standards for Basic Intraoperative Monitoring, Conduction Anesthesia in Obstetrics, and Postanesthesia Care.

Baby Barash will not wake you in the middle of the night for feeding. But, if you need to review at 2 AM the anesthetic considerations for a patient with porphyria, or determine the proper dose of amrinone, just reach for the "Baby" in your pouch.

The material is presented cogently and tersely. Most facts are tabulated or arranged in algorithms, "designed for rapid acquisition of essential information" (from the Preface to the handbook). A review of 100 consecutive pages revealed no less than 71 pages with summary tables or graphic material (illustrations, diagrams, trace recordings, dose-response curves).

The drug list is particularly useful. It provides both the generic and brand name of each drug, its common uses, doses for various routes of administration, site of clearance, and interaction/toxicity.

On the inside of the front cover there is a protocol for failed rapid-sequence intubation, and on the inside of the back cover there is a procedure for extinguishing airway fires. The editors, apparently, placed these important guidelines in a prominent place for quick access. However, this reviewer doubts that clinicians would look for guidelines while the patient's airway is up in flames. Perhaps more appropriate use for the covers would be the FDA-endorsed anesthesia machine checklist, and a list of drugs and dosages for advanced cardiac life support.

As is commonly the case with books of this magnitude, there is no escape from typographical errors. Anemias and rheumatoid arthritis are classified under rare coexisting diseases. Table 37-2 incorrectly states that arterial distensibility is increased in elderly patients. Mivacurium is misspelled in Table 18-2. Table 10-5 incorrectly states the dextrose content of crystalloid solutions (a 5% dextrose solution contains 5 g of dextrose in 100 mL).

A major advantage of a handbook is portability. This particular handbook brings important anesthesia information to the patient's bedside. However, despite its reduced size, it might still be inconvenient to use it in the operating room. Perhaps the ultimate solution would be an electronic

version of this handbook. As the anesthesia machine becomes more and more "microchipped," it should eventually become possible to store the "Baby" electronically in every machine. Various management protocols would then become instantaneously available at a touch of a keyboard.

Isaac Azar, MD Beth Israel Hospital New York, New York

Books Received

Receipt of the books listed below is acknowledged. Selected books from this list will be reviewed in future issues of the Journal.

The Journal solicits reviews of new books from its readers. If you wish to submit a review, before proceeding please send a letter of intent, identifying the book in question, to Dr. Norlg Ellison, Department of Anesthesia, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104. The Journal reserves the right of final decision on publication.

Cheng EV, Kay J, eds. Manual of Anesthesia and Medically Compromised Patient. Philadelphia: J.B. Lippincott, 1991, 704 pp, \$42.50.

Goshen-Gottstein E. Recalled to Life, The Story of a Coma. New Haven: Yale University Press, 1990, 208 pp, \$25.00.

Grenvik A, Downs J, Räsänen J, Smith R, eds. Mechanical Ventilation and Assisted Respiration: Past, Present, and Future. Volume 1, No. 1 of Contemporary Management in Critical Care series. New York: Churchill Livingstone, 1991, 190 pp, \$85.00 subscription for four issues or \$32.50 for a single issue.

Lebowitz PW, ed. Multidisciplinary Pain Management. Volume 29, No. 1 of International Anesthesiology Clinics, Boston: Little Brown, 1991, 109 pp, \$81.00 subscription for four issues or \$38.00 for a single issue.

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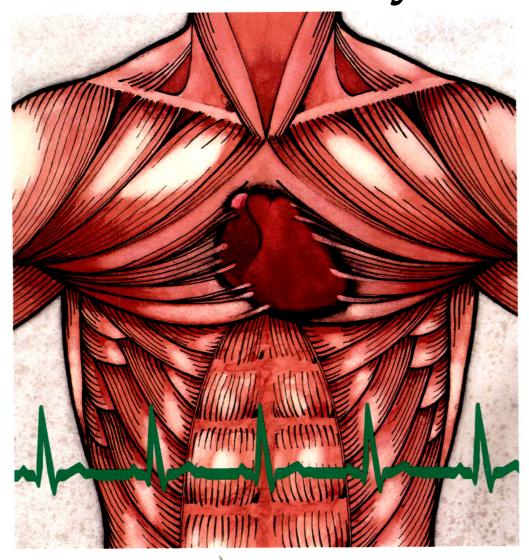
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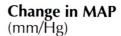


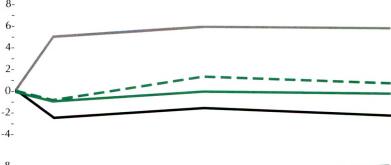
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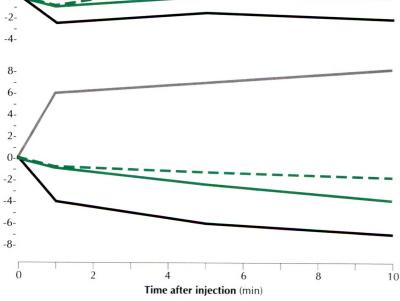
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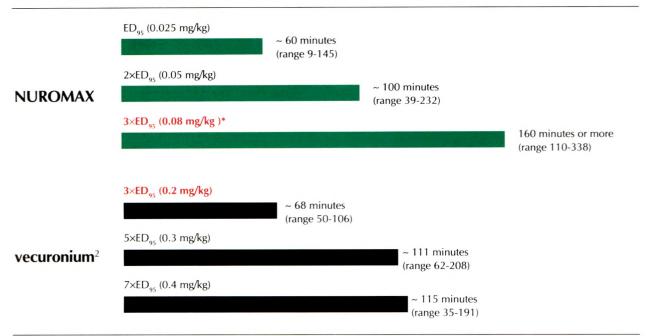
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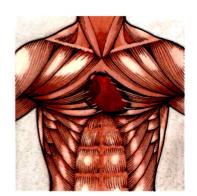
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Dozacunium chioride is a mixture of three *lanes, leans* stereoisomers, a *d* pair $[(1R, 1^{\circ}R, 2S, 2^{\circ}S)]$ and $(1S, 1^{\circ}S, 2R, 2^{\circ}R)]$ and a meso form $(1R, 1^{\circ}S, 2S, 2^{\circ}R)$.

Nuromax Injection is a starile, non-pyrogenic aqueous solution (pH 3.9 to 5.0) containing dexacurium chloride equivalent to 1 mg/mil, doxacurtum in Water for Injection. Hydrochloric acid may have been added to adjust pH. Nuromax Injection contains 0.9% w/v benzyl alcohol.

CLINICAL PHARMACCLOGY: Nuromex binds competitively to cholinergic receptors on the motor end-plate to antagonize the action of acetylcholine, resulting in a block of nauromuscular transmission. This action is artagonized by acetylcholinesterase inhibitions, such as neostigmine.

Pharmacodynamics: Nuromax is approximately 2.5 to 3 times more potent than parauronium and 10 to 12 times more potent than parauronium and 10 to 12 times more potent than metocurine. Nuromax in doses of 1.5 to 2 x ED₈₅ has a clinical duration of action (range and writefully) similar to that of equipotent doses of parauronium and metocurine (historic data and timilar comparison). The average ED₈₅ (dose required to produce 85% suppression of the adductor policie muscle twitch response to ulner nerve stimulation) of Nuromax is 0.025 mg/kg (range: 0.020 to 0.033) in adults receiving balanced anesthesia.

The onset and clinically effective duration (time from injection to 25% recovery) of Nuromax administered alone or after succiny/choline during stable balanced enesthesia are shown in Table 1.

TABLE 1 Pharmscodynamic Dose Response* Balanced Anesthesis

	hnifial Nuromax Dose (mo/kg)		
	0.025 ¹	0.05	0.08
	(n=34)	(n=27)	(n=9)
Time to Maximum	9.3	6.2	3.5
Block (min)	(5.4-16)	(2.5-13)	(2.4-5)
Clinical Duration (min)	55	100	180
(Time to 25% Recovery)	(9-1 45)	(39-232)	(110-336)

Values shown are means (range).
 Nuromex administered after 10% to 100% recovery from an intubating does of succinylcholine.

Initial doses of 0.05 mg/kg (2 x ED $_{\rm pc}$) and 0.08 mg/kg (5 x ED $_{\rm pc}$) humanax administered during the induction of thiopental-nercotic anesthesia produced good-to-excellent conditions for trached intubation in 5 minutes (13 of 15 cases studied) and 4 minutes (8 of 9 cases studied) (which are before maximum block), respectively.

As with other long-acting agents, the clinical duration of neuromuscular block associated with Nuromax shows considerable interpatient variability. An analysis of 390 cases in U.S. clinical trials utilizing a variety of premedications, varying lengths of surgery, and various anesthatic agents, indicates that approximately twofaints of the patients had ctinical durations within 30 minutes of the duration predicted by dose (based on mg/kg actual body weight). Patients ≥ 80 years old are approximately twice as likely to experience prolonged clinical duration (30 minutes longer than predicted) than patients < 60 years old; thus, care should be used in older patients when protonged recovery is undestrable (see Gerlatric Use subsection of PRECAUTIONS and Individualization of Dosages subsection of CLINICAL PHARMACOLOGY). In addition, obese patients (patients weighing ≥ 30% more than ideal body weight for height) were almost twice as likely to experience prolonged clinical duration than non-obese patients; therefore, doeing should be based on ideal body weight (IEW) for obese patients (see individualization of Dosages subsection of CLINICAL PHARMACOLOGY).

The mean time for sportaneous T₁ recovery from 25% to 50% of control following initial closes of Nuromax is approximately 26 minutes (range: 7 to 104, n=253) during balanced anesthesia. The mean time for sportaneous T₁ recovery from 25% to 75% is 64 minutes (range: 14 to 184, n=184).

Most patients receiving Nuromax in clinical triels required pharmacologic reversal prior to full spontaneous recovery from neuromuscular block (see Antagoniam of Neuromuscular Block subsection of OVERDOSAGE); therefore, relatively few data are available on the time from injection to 95% spontaneous recovery of the twitch response. As with other long-acting neuromuscular blocking agents, Nuromax may be associated with prolonged times to full spontaneous recovery. Following an initial dose of 0.025 mg/kg Nuromax, some patients may require as long as 4 hours to exhibit full spontaneous recovery.

Cumulative neuromuscular blocking effects are not associated with repeated administration of main doses of Nuromax at 25% T₁ recovery. As with initial doses, however, the duration of action following maintenance doses of Nuromax may vary considerably among patients.

The Nurromax ED₉₅ for children 2 to 12 years of age receiving halothane anesthesia is approximately 0.03 mg/tg. Children require higher Nuromax doses on a mg/tg basis than adults to achieve comparable levels of block. The oraset time and duration of block are shorter in children than adults. During halothane anesthesia, doses of 0.03 mg/kg and 0.05 mg/kg Nuromax produce maximum block in approximately 7 and 4 minutes, respectively. The duration of clinically effective block is approximately 30 minutes after an initial dose of 0.03 mg/kg and approximately 45 minutes after 0.05 mg/kg. Nuromax has not been studied in children below the age

The neuromuscular block produced by Nuromax may be antagonized by anticholimesterase agents. As with other nondepolarizing neuromuscular blocking agents, the more profound the neuromuscular block at reversal, the longer the time and the greater the dose of anticholinesterase required for recovery of neuromuscular function.

Hernodynamics: Administration of Nuromax doses up to and including 0.08 mo/kg (~3 x ED_{ex}) over 5 to 15 seconds to healthy adult patients during stable state belanced anesthesis and to patients with serious cardiovascular disease undergoing coronary artery bypase graffing, cardiac valvular repair, or vascular repair produced no dose-related effects on mean arterial blood pressure (MAP) or heart rate (HR).

No dose-related changes in MAP and HR were observed following administration of up to 0.05 mg/kg Nuromax over 5 to 15 seconds in 2- to 12-year-old children receiving halothane anesthesia.

Doses of 0.03 to 0.06 mg/kg (1.2 to 3 x ED₂₅) were not associated with dose-dependent changes in mean pleama histamine concentration. Clinical experience with more than 1,000 patients indicates that adverse experiences typically associated with histamine release (a.g., bronchospasm, hypotension, technocure, cutaneous flushing, unicaria, etc.) are very rare following the administration of Nuromax (see ADVERSE

Phermacokinetics: Phermacokinetic and pharmacodynamic results from a study of 24 healthy young adult patients and 8 healthy elderly patients are summarized in Table 2. The pharmacokinetics are linear over the doesage range tested (Le., plasma concentrations are approximately proportional to does). The pharmaco-kinetics of Naromax are similar in healthy young adult and elderly patients. Some healthy elderly patients tend to be more sensitive to the neuromuscular blocking effects of Naromax than healthy young adult patients receiving the same does. The time to maximum block is longer in elderly patients then in young adult patients (11.2 minutes versus 7.7 minutes at 0.025 mg/kg Nuromax). In addition, the ctrically effective durations of block are more variable and tend to be longer in healthy elderly patients than in healthy young adult patients receiving

TABLE 2 Pharmacokinetic and Pharmacodynamic Para ers' of Nuromex in Young Adult and Elderly Patients : Parameters' of Nuron (Isotumne Anesthesia)

	Healthy Young Adult Patients			Healthy Elderly Patients	
Parameter	(22 to 49 yrs)			(67 to 72 yrs)	
r carellation	0.025 mg/kg	0.05 mg/kg	0.08 mg/kg	0.025 mg/kg	
	(n=8)	(n=6)	(n=8)	· (n=8)	
t _{se} elimination	86	123	98	96	
(min)	(25-171)	(61-163)	(47-163)	(50-114)	
Volume of Distribution at	0.15	0.24	0.22	0.22	
Steady State (L/kg)	(0.10-0.21)	(0.13-0.30)	(0.16-0.33)	(0.14-0.40)	
Plasma Clearance	2.22	2.62	2.53	2.47	
(mL/min/kg)	(1.02-3.95)	(1,21-5.70)	(1.88-3.38)	(1.58-3.80)	
Maximum Block	97	100	100	96	
(%)	(68-100)	(100-100)	(100-100)	(90-100)	
Clinically Effective Duration of Block ² (min)	68	91	177.	97	
	(35 -9 0)	(47-132)	(74-268)	(36-179)	

1 Values shown are means (rance).

2 Time from injection to 25% recovery of the control twitch height.

2 times from rejection to 25% recovery of the control teach neight.

Table 3 summarizes the pharmacokinetic and pharmacodynamic results from a study of 9 healthy young adult patients, 8 patients with end-stage kidney disease undergoing kidney transplentation, and 7 patients with end-stage kidney disease; in addition, these patients suggest that a longer type can be expected may be more sensitive to the neuronuscular blocking effects of Nuromeo. The time to meadment block was slightly longer and the clinically effective duration of block was protonged in patients with end-stage kidney disease

Pharmacokinetic and Pharmacodynemic Parametera' of Nuromex in Healthy Patients and in Patients Undergoing Kldney or Liver Transplantation (Isoliurane Aneshesia)

Parameter	Heelithy Young	Kidney	Liver	
	Adult Patients	Transplant Patients,	Transplant Patients	
radioux	0.015 mgAvg	0.015 m g/k g	0.015 mg/kg	
	(n=9)	(n=8)	(n=7)	
t _{us} elimination	99	221	115	
(min)	(48-193)	(84-582)	(69-148)	
Volume of Distribution at	0.22	0.27	0.29	
Steady State (L/kg)	(0.11-0.43)	(0.17-0.55)	(0.17-0.35)	
Plasma Clearance	2.66	1.23	2.30	
(mL/min/kg)	(1.35-8.86)	(0.48-2.40)	(1.96-3.05)	
Meximum Block	86	98	70	
(%)	(59-100)	(95-100)	(0-100)	
Clinically Effective Duration of Block (min)	38	80	52	
	(19-80)	(29-133)	(20-91)	

1 Values shown are means (range).

It vanues encover are means (range).

No data are available from patients with liver disease not requiring transplentation. There are no significant absentions in the pharmacokinetics of Nuromex in tiver transplant patients. Sensitivity to the neuromuscular blocking effects of Nuromax was highly variable in patients undergoing liver transplantation. Three of 7 petients developed ≤ 50% block, indiceting that a reduced sensitivity to Nuromax may occur in such patients. In the patients who developed > 50% neuromascular block, the time to maximum block and the clinically effective duration tended to be longer than in healthy young adult patients (see individualization of Desages subsection of CLINECAL PHARMACOLOGY).

Consecutively administered maintenance doses of 0.005 mg/kg Nuromax, each given at 25% T₁-recovery following the preceding dose, do not result in a progressive increase in the pleama concentration of doxecunium or a progressive increase in the depth or duration of block produced by each dose.

Nuromax is not metabolized in vitro in fresh human plasma. Plasma protein binding of Nuromax is approximately 90% in human plesma.

In vivo data from humans passate that Nuromax is not metabolized and that the major estimation pathway is excretion of unchanged drug in urine and bile. In studies of healthy adult patients, 24% to 38% of an administered dose was recovered as parent drug in urine over 6 to 12 hours after dosting. High bile concentrations of Nuromax (relative to pleasma) have been found 35 to 90 minutes after administrion. The overall extent of billiary excretion is unknown. The data derived from analysis of human urine and bille are consistent with data from in who studies in the rat, cet, and dog, which indicate that all of an administered dose of Nuromax is recovered as parent drug in the urine and bile of these species.

Individualization of Dosagos: In elderly patients or patients who have impaired renal function, the potential for a prolongation of block may be reduced by decreasing the initial Nuromax dose and by librating the dose to achieve the desired depth of block. In obese patients (patients weighing > 30% more than ideal body weight for height), the Nuromax dose should be determined using the patient's ideal body weight (IBW), according to the fallowing formulae

Men: IBW in kg = [106 + (6 x inches in height above 5 feet)]/2.2

Women: IBW in kg = [100 + (5 x inches in height above 5 feet)/2.2

Dosage requirements for patients with severe fiver disease are variable; some patients may require a higher than normal initial Nuromex dose to active clinically effective block. Once adequate block is established, the clinical duration of block may be protonged in such patients relative to patients with normal liver function.

As with pencuronium, metocurine, and vecuronium, resistance to Nuromax, manifested by a reduced intensity ander shortened duration of block, must be considered when Nuromex is selected for use in petients receiving phenyloin or carbamizzepine (see Drug Interactions subsection of PRECAUTIONS).

presynon or cardemazespine (see until interactions subsection of PPECARU IDANS).

As with other nondepolarizing neuromuscular blocking agents, a reduction in desage of Nuromax must be considered in cachectic or debilitated petients, in patients with neuromuscular diseases, severe electrolyte abnormalities, or cardinomaticis, and in other patients in whom potentiation of neuromuscular block or difficulty with reversal is anticipated, increased doses of Nuromax many be required in burn patients (see PRE-

INDICATIONS AND USAGE: Nuromax is a long-acting neuromuscular blocking agent, indicated as an adjunct to general anesthesia, to provide skeletal muscle relevation during surgery. Nuromax can also be used to provide skeletal muscle relexation for endotraches! intubation.

CONTRAINDICATIONS: Nuromax is contraindicated in petients known to have hypersensitivity to it.

CONTRADIDICATIONS: Nuronax is contraindicated in pedents known to have hypersonatively to it.

WARNINGS: NUROMAX SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR
UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH THE DRUG'S
ACTIONS AND THE POSSIBLE COMPLICATIONS OF ITS USE. THE DRUG SHOULD NOT BE
ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ATTRIFICIAL RESPRATION, OXYGEN THERPAY,
AND AN ANTAGONIST ARE WITHIN MIMEDIATE REACH, IT IS RECOMMENDED THAT CLINICIANS
ADMINISTERING LONG-ACTING NEUROMAUSCULAR BLOCKING AGENTS SUCH AS NUROMAX EMPLOY
A PERIPHERAL NERVE STUMULATOR TO MONITOR DRUG RESPONSE, NEED FOR ADDITIONAL

PERIPHERAL NERVE STUMULATOR TO MONITOR DRUG RESPONSE, NEED FOR ADDITIONAL RELAXANTS, AND ADEQUACY OF SPONTANEOUS RECOVERY OR ANTAGONISM.

NURCHARX HAS NO KNOWN EFFECT ON CONSCIOUSNESS, PAIN THRESHOLD, OR CEREBRATION. TO AVOID DISTRESS TO THE PATIENT, NEUROMAUSCULAR BLOCK SHOULD NOT BE INDUCED BEFORE UNCONSCIOUSNESS.

Nurcriax injection is acidic (pH 3.9 to 5.0) and may not be compatible with alkaline solutions having a pH greater than 8.5 (e.g., parbiturate solutions)

Nuromax Injection contains benzyl alcohol. In newborn infants, benzyl alcohol has been associated with an increased incidence of neurological and other complications which are sometimes tatal. See Pediatric Use

PRECAUTIONS: General: Nuromax has no clinically significant effects on heart rate; therefore, Nuromax will not counteract the bradycardia produced by many anesthetic agents or by vagel stimulation.

Neuromuscular blocking agents may have a profound effect in patients with neuromuscular diseases (e.g., myasthenia gravis and the myasthenic syndrome). In these and other conditions in which prolonged neuromuscular block is a possibility (e.g., carcinomatosis), the use of a perhyberal nerve stimulator and a small test dose of Nuromax is recommended to assess the level of neuromuscular block and to moritor dosage requirements. Shorter acting muscle relaxants than Nuromax may be more suttable for these patients.

Resistance to nondepotenting neuromuscular blocking agents may develop in patients with burns depending upon the time elepsed since the Injury and the size of the burn. Nuromax has not been studied in patients with burns.

Acid-base end/or serum electrolyte abnormatities may potentiate or antagonize the action of neuromuscular blocking agents. The action of neuromuscular blocking agents may be enhanced by magnesium salts administered for the management of loxernia of pregnancy.

Nuromex has not been studied in patients with asthma.

No data are available to support the use of Nuromax by intramuscular injection.

Renal and Hapetrio Dissesse: Nuromax has been studied in patients with end-stage kidney (n=8) or liver (n=7) disease undergoing transplantation procedures (see CLINICAL PHARMACOLOGY). The possibility of protonged neuromuscular block in patients undergoing meal transplantation and the possibility of seriable onset and duration of neuromuscular block in patients undergoing liver transplantation must be considered when Nummay is used in such pelleris.

where mutuations are used in south process.

Obsetty: Administration of Nuromax on the basis of actual body weight is associated with a prolonged duration of action in obser patients (patients weighing > 30% more than ideal body weight for height) (see CLINICAL PHARMACOLOGY). Therefore, the dose of Nuromax should be based upon ideal body weight in obser patients (see individualization of Dosages subsection of CLINICAL PHARMACOLOGY).

Melignamt Hyperthermia (MH): In a study of Mil-succeptible pigs, Nuromax did not trigger MH. Nuromax has not been studied in MH-succeptible patients. Since MH can develop in the absence of established triggering egents, the clinician should be prepared to recognize and treat MH in any patient scheduled for general

Long-Term Use in the Intensive Care Unit (ICU): No data are available on the long-term use of Nuromax in patients undergoing mechanical vanilation in the ICU.

Drug Interactions: Prior administration of succinylcholine has no clinically important effect on the neuromuscular blocking action of Nuromex.

The use of Nuromax before succinylcholine to attenuate some of the side effects of succinylcholine has not heen studied.

There are no clinical data on concomitant use of Nuromax and other nondepolarizing neuromuscular blocking

Isofturane, enflurane and helothane decrease the ${\rm ED_{80}}$ of Nuromax by 30% to 45%. These agents may also prolong the clinically effective duration of action by up to 25%.

Other drugs which may enhance the neuromuscular blocking action of nondepolarizing agents such as Nuromax Include certain antibiotics (a.g., aminophycosides, tetracyclines, bactiracin, polympains, lincomycin, clindamycin, cotain, and sodium collatimethale), megnesium salts, fithum, local anesthetics, proceinamide, and

As with some other nondepolarizing neuromuscular blocking agents, the time of onset of neuromuscular block induced by Nuromax is lengthened and the duration of block is shortened in petients receiving phenytoin or

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis and fertility studies have not been performed. Nuromax was evaluated in a battery of four short-term mutagenicity tests. It was non-mutagenic in the Ames Saimonella assay, in the investment of the four and in the human lymphocyte assay. In the investment of the human lymphocyte assay, in the investment increases in the invitedness of structural abnormalities, relative to vehicle controls, were observed in male ratio dosed with 0.1 mg/kg (0.625 mg/m²) Nuromax and sacrificed at 6 hours, but not at 24 or 48 hours, and in lemale ratio dosed with 0.2 mg/kg (1.25 mg/m²) Nuromax and sacrificed at 6 hours, but not at 24 or 48 hours, and in lemale ratio dosed with 0.2 mg/kg (1.25 mg/m²) Nuromax. sacrificed at 6 hours, but not at 24 or 48 hours, and in ternale ratis dosed with 0.2 mg/kg (1.25 mg/m²) Nutromax and sacrificed at 24 hours, but not at 6 or 48 hours. There was no increase in structural abnormalities in either male or female ratis given 0.3 mg/kg (1.875 mg/m²) Nutromax and sacrificed at 6, 24, or 48 hours. Thus, the incidence of abnormalities in the *in vivo* rat bone marrow cytogenetic easiey was not dose-dependent and, therefore, the likelihood that the observed abnormalities were treatment-related or clinically significant is often therefore. Teratogenic Effects: Pregnancy Category C. Teratogy testing in nonventilated, pregnant ratis and mice treated subcutaneously with maximum subparalyzing doses, of Nutromax revealed no maternal or fetal toxicity or teratogenic effects. There are no adequate and well-controlled studies of Nutromax in pregnant

women. Because arimal studies are not always predictive of human response and the doses used were subparalyzing, Nuromax should be used during pregnancy only if the potential benefit justifies the potential risk

Labor and Delivery: The use of Nuromex during labor, veginal delivery, or cesarean section has not been studied. It is not known whether Nuromex administered to the mother has immediate or delayed effects on the fetus. The durifion of action of Nuromex exceeds the usual duration of operative obstetrics (cesarean section). Therefore, Nuromex is not recommended for use in patients undergoing C-section.

Nursing Mothers: It is not known whether Nuromax is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised following Nuromax administration to a nursing

Pediatric Use: Nuromax has not been studied in children below the age of 2 years. See CI,INICAL PHAPMACOLOGY and DOSAGE AND ADMINISTRATION for clinical experience and recommendations for use in children 2 to 12 years of soe.

Gertatric Use: Nuromax has been used in etderty patients, including patients with significant cardiovescular disease. In etderty patients the onset of maximum block is slower and the duration of neuromuscular block produced by Nuromax is more variable and, in some cases, longer than in young adult patien Pharmacodynamics and individualization of Dosages subsections of CLINICAL PHARMACOLOGY).

ADVERSE REACTIONS: The most requent adverse stoscooks of current Pharmacoccusts as a class consists of an extension of the pharmacological action beyond the time needed for surgery and anesthesis. This effect may very from skeletal muscle weakness to profound and protonged skeletal muscle paralysis resulting in respiratory insufficiency and sones which require manual or mechanical verification until recovery is judged to be clinically adequate (see OVERDOSAGE). Inadequate reversed of neuromuscular block from Nuromax is possible, as with all nondepotarizing agents. Protonged neuromuscular block and inadequate reversal may lead to postmere the commisciple of the protonged of the to postoperative complications.

Observed in Clinical Trials: Adverse experiences were uncommon among the 1034 surgical petients and volunteers who received Nuronars and other drugs in U.S. chrical studies in the course of a wide variety of procedures conducted during balanced or inhabitional enesthesis. The following adverse experiences were reported in petients administered Nuronax (all events judged by investigators during the clinical studies to have a contible causal relationship):

Incidence Greater than 1% - None

incidence Less than 1% -

hypoteneion," flushing," ventricular fibrillation, myocardial infarction branchospasm, wheezing Continuoundor

Respiratory: urilcaria, injection site reaction Dermatological:

Nonspecific

diplopts difficult neuromuscular block revenual, prolonged drug effect, fever

Reports of ventricular fibrillation (n=1) and invocardial infanction (n=1) were limited to ASA Class 3-4 patients undergoing cardiac surgery (n=142)

0.3% incidence. All other reactions unmerked were ≤ 0.1%.

OVERDOSAGE: Overdosage with neuromuscular blocking agents may result in neuromuscular block beyond the time needed for surgery and anesthesia. The primary treatment is maintenance of a patent already and controlled vertilation until recovery of normal neuromuscular function is assured. Once evidence of recovery from neuromuscular block is observed, further recovery may be facilitated by administration of an anticholinesterase agent (e.g., neostigmine, edrophonium) in conjunction with an appropriate anticholinergic agent (see Antagonism of Neuromuscular Blook).

Antagonism of Neuromuscular Block: ANTAGONISTS (SUCH AS NEOSTIGMINE) SHOULD NOT BE ADMINISTERED PRIOR TO THE DEMONSTRATION OF SOME SPONTANEOUS RECOVERY FROM NEUROMUSCULAR BLOCK. THE USE OF A NERVE STIMULATOR TO DOCUMENT RECOVERY AND ANTAGONISM OF NEUROMUSCULAR BLOCK IS RECOMMENDED. TATA SHOULD BE > ZERO BEFORE ANTAGONISM IS ATTEMPTED.

In an analysis of patients in whom antagonism of neuromuscular block was evaluated following administration of in an animpse of neoesignitine averaging 0.08 mg/kg (range: 0.05 to 0.075) administrated at approximately 25% T_1 , aportaneous recovery during belanced anesthesia, 71% of patients exhibited $T_d T_1 \geq 0.7$ before monitoring was discontinued. For these patients, the mean time to $T_d T_1 \geq 0.7$ was 19 minutes (range: 7 to 55). As with other long-acting nondepolarizing neuromuscular blocking agents, the time for recovery of neuromuscular function blowing administration of neestigmine is dependent upon the level of residual neuromuscular block at the time of attempted reversal; longer recovery times than those cited above may be anticipated when neestigmine is administered at more profound levels of block (ℓe , at < 25% T_1 recovery).

Patients should be evaluated for adequate clinical evidence of antagonism, e.g., 5-second head lift, and grip strength. Ventilation must be supported until no longer required. As with other neuromuscular blocking agents, physicians should be alert to the possibility that the action of the drugs used to antagonize neuromuscular block may wear off before the effects of Nuromax on the neuromuscular junction have declined sufficiently.

Antagonism may be delayed in the presence of debilitation, carcinomatosis, and the concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular block or separately cause respiratory depression (see Drug Interactions subsection of PRECAUTIONS). Under such circumstances the management is the same as that of prolonged neuromuscular block.

In clinical triefs, a dose of 1 mg/kg edrophonium was not as effective as a dose of 0.06 mg/kg neostigmine in antagonizing moderate to deep levels of neuromuscular block (i.e., < 60% T_1 recovery). Therefore, the use of 1 mg/kg edrophonium is not recommended for reversal from moderate to deep levels of block. The use of igmine has not been studied.

DOBAGE AND ADMINISTRATION: NUROMAX SHOULD ONLY BE ADMINISTERED INTRAVENOUSLY.

Nuromex, like other long-acting neuromuscular blocking agents, displays variability in the duration of its effect. The potential for a prolonged clinical duration of neuromuscular block must be considered when Nuromax is selected for administration. The desage information provided below is intended as a guide only. Doses should be individualized (see Individualization of Doseges subsection of CLINICAL PHARMACOLOGY). Factors that may warrant doeage adjustment include: advancing age, the presence of kidney or liver disease, or obesity (patients weighing ≥ 30% more than ideal body weight for height). The use of a peripheral nerve stimulator will permit the most advantageous use of Nuromex, minimize the possibility of overdosage or underdosage, and assist in the evaluation of recovery.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Adults: Initial Doses: When administered as a component of a thiopental/narcotic induction paraction as well as for production of long-duration neuromuscular block during surgery, 0.05 mg/kg (2 x ED₃₅). Nuromax produces good-to-excellent conditions for tracheal intubation in 5 minutes in approximately 90% of patients. Lower doses of Nuromax may result in a longer time for development of satisfactory intubation conditions. Clinically effective neuromuscular block may be expected to less approximately 100 minutes on average (range: 39 to 232) following 0.05 mg/kg Nuromax administered to patients receiving balanced

An initial Nuromax dose of 0.06 mg/kg (3 x ED_{pd}) should be reserved for instances in which a need for very protonged neuromuscular block is articipated. In approximately 90% of patients, good-to-excellent intubation conditions may be expected in 4 minutes efter this dose; however, clinically effective block may be expected to persist for as long as 160 minutes or more (range: 110 to 338) (see CLINICAL PHARMACOLOGY).

If Nuromex is administered during steady-state isofarrans, enforceme, or halothane anesthesia, reduction of the Nurromax dose by one-third should be considered.

When succinvictorine is administered to facilitate tracheal intubation in patients receiving balanced anesth an inflied does of 0.025 mg/kg (ED₆₅) furrormax provides about 60 minutes (range: 9 to 145) of clinically effective neuromuscular block for surgery. For a longer duration of action, a larger initial dose may be administered.

Meintenence Doses: Maintenance dosing will generally be required about 60 minutes after an initial dose of 0.025 mg/kg Nuromax or 100 minutes after an initial dose of 0.05 mg/kg Nuromax during balanced anasthesta. Repeated maintenance closes administered at 25% T₁ recovery may be expected to be required at relatively regular intervals in each patient. The interval may vary considerably between patients. Maintenance closes of 0.005 and 0.01 mg/kg Nuromax each provide an average 30 minutes (range: 9 to 57) and 45 minutes (range: 14 to 106), respectively, of additional clinically effective neuromuscular block. For shorter or longer desired durations, smaller or larger maintenance doses may be administered.

Chilidren: When administered during halothane anesthesia, an initial dose of 0.03 mg/kg (EDgs) produces maximum neuromuscular block in about 7 minutes (range: 5 to 11) and clinically effective block for an average of 30 minutes (range: 12 to 54). Under hallothene ensesthesia, 0.05 mg/kg produces maximum block in about afficiency (range: 2 to 10) and clinically effective block for 5 minutes (range: 30 to 80). Malinterance doses are generally required more frequently in children than in adults. Because of the potentialing effect of hallothane seen in adults, a higher dose of Nuromax may be required in children receiving balanced anesthesia than in children receiving halothane anesthesia to achieve a comparable cruset and duration of neuromuscular block. Nuromax has not been studied in children below the age of 2 years.

Competibility: Y-elle Administration: Nuromax injection may not be compatible with alkaline solutions with a pH greater then 8.5 (e.g., barbiturate solutions).

Nuromax is compatible with:

5% Devirose injection USP 0.9% Sodium Chtodde Injection USP 6% Devirose and 0.9% Sodium Chloride Injection USP Lactated Pinger's Injection USP

6% Decirces and Lactated Ringer's Injection Sulernia" (suriorismi dictate) Injection, diluted as directed Allernia" silainmial Injectioninola Injection, diluted as directed Subtimizer" (femiany) citrate) Injection, diluted as directed

Dilution Stability: Nuromax diluted up to 1:10 in 5% Dextrese Injection USP or 0.9% Sodium Chloride Injection USP has been shown to be physically and chemically stable when stored in polypropylane syringes at 5° 25°C (41° to 77°F), for up to 24 hours. Since dilution diminishes the preservative effectiveness of ben alcohol, exeptic techniques should be used to prepare the diluted product. Immediate use of the diluted product is preferred, and any unused portion of diluted Nuromax should be discarded after 8 hours...

HOW SUPPLIED: Nuromax Injection, 1 mg doxecurium in each ml..

5 ml. Multiple Dose vials containing 0.9% w/v benzyl alcohol as a preservative (see WARNINGS). Tray of 10

STORAGE: Store Nuromax Injection at room temperature of 15° to 25°C (59° to 77°F). DO NOT FREEZE. U.S. Patent No. 4701460

- 1. Emmott RS, Bracey BJ, Goldhill DR, Yate PM, Flynn PJ. Cardiovascular effects of doxacurlum, pancuronium and vecuronium in anaesthetized patients presenting for coronary artery bypass surgery. Br J Anaesth.
- 2. Tullock WC, Diana P, Cook DR, et al. Neuromuscular and cardiovascular effects of high-dose vecuronium. Anesth Anelly, 1990;70:88-90.
- Sloops CM, Curis CA, Kovach DA, et al. Hemodynamic effects of doxacurium chloride in patients receiving oxygen sufentaril anesthesia for coronary arisny bypass grafting or valve replacement. Anasthesiology. 1986;99:385-370.



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□ Original articles describe in 3000 words or less clinical or laboratory investigations.
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after continuous spinal anesthesia. Anesth Analg 1991;72:275-81. 2. Personal author(s) of books and monographs	Abbreviations			
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logic physiology: mechanisms of disease. Philadelphia: WB Saunders, 1974:457–72.	☐ Consult the following sources for abbreviations: 1. CBE Style Manual Committee. Council of Biology Editors style Transport of Transport of Biology Editors style Transport of Tran			
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7.

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VERSED* (midazolam HCl/Roche) № INJECTION

Before prescribing, please consult complete product information, a summary of which follows:

Intravenous VERSED has been associated with respiratory depression and respiratory arrest, especially when used for consclous sedation. In and respiratory arrest, especially when used for considuous seation. In some cases, where this was not recognized promptly and treated effectively, death or hypoxic encephalopathy has resulted. Intravenous VERSED should be used only in hospital or ambulatory care settings, including physicians' offices, that provide for continuous monitoring of respiratory and cardiac function. Immediate availability of resuscitative

respiratory and cardiac function. Immediate availability of resuscitative drugs and equipment and personnel trained in their use should be assured. (See WARNINGS.)

The initial intravenous dose for conscious sedation may be as little as 1 mg, but should not exceed 2.5 mg in a normal healthy adult. Lower doses are necessary for older (over 60 years) or debilitated patients and in patients receiving concomitant nercotics or other CNS depressants. The initial dose and all subsequent doses should never be given as a bolus; administer over at least 2 minutes and allow an additional 2 or more minutes to fully evaluate the sedative effect. The use of the 1 mg/mL formulation or dilution of the 1 mg/mL or 5 mg/mL formulation is recommended to facilitate slower injection. Consult complete product information under DOSAGE AND ADMINISTRATION for complete dosing information.

CONTRAINDICATIONS: Patients with known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma; may be used in open angle glaucoma only if patients are receiv-

glaucoma; may be used in open angle glaucoma only it patients are receiving appropriate therapy.

WARNINGS: Never use without Individualization of dosage. Prior to IV use in any dose, ensure immediate availability of oxygen, resuscitative equipment and skilled personnel for maintenance of a patent alimay and support of ventilation. Continuously monitor for early signs of underventilation or apnea, which can lead to hypoxia/cardiac arrest unless effective countermeasures are taken immediately. Vital signs should continue to be monitored during the recovery period. Because IV VERSED depresses respiration, and opioid agonists and other sedatives can add to this depression, it should be administered as an induction agent only by a person trained in general anesthesia and should be used for conscious sedation only in the presence of personnel skilled in early detection of underventilation, maintaining a patent airway and supporting ventilation. For conscious sedation, do not administer IV by rapid or single bolus. Serious cardiorespiratory adverse events have occurred. These have included respiratory depression, apnea, respiratory arrest and/or cardiac arrest, sometimes resulting in death. There have been rare reports of hypotensive episodes requiring treatment during or after diagnostic or surgical manipulations in patients who have received VERSED. Hypotension occurred more frequently in the consclous sedation studies in patients premedicated with narcotic. Reactions such as agitation, involuntary movements, hyperactivity and combativeness have been reported. These may be due to inadequate or excessive dosing or improper administration; however, the possibility of cerebral hypoxia or true paradoxical reactions should be considered. Should these reactions occur, response to each dose of VERSED and all other drugs should be evaluated before proceeding.

Concomitant use of barbiturates, alcohol or other CNS depressants may increase the risk of underventilation or apnea and may contribute to perfound and/or prolonged ing appropriate therapy.

WARNINGS: Never use without individualization of dosage. Prior to IV

longed effect.

Do not administer in shock, coma, acute alcohol intoxication with depression of vital signs. Particular care should be exercised in the use of IV VERSED in patients with uncompensated acute illnesses, such as severe fluid or electrolyte disturbances.

Guard against unintended intra-arterial injection; hazards in humans unknown. Avoid extravasation.

unknown. Avoid extravasation.

Gross tests of recovery from the effects of VERSED cannot alone predict reaction time under stress. This drug is never used alone during anesthesla, and the contribution of other perioperative drugs and events can vary. The decision as to when patients may engage in activities requiring mental alertness must be individualized; it is recommended that no patient should operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until the day after anesthesia, whichever is

Usage in Pregnancy: An increased risk of congenital malformations associated with the use of benzodlazepines (diazepam and chlordlazepoxide) has been suggested in several studies. If VERSED is used during pregnancy, apprise the patient of the potential hazard to the

PRECAUTIONS: General: Decrease intravenous doses in elderly and debilitated patients. These patients will also probably take longer to recover com-pletely after VERSED for induction of anesthesia. VERSED does not protect against increased intracranial pressure or against

VEHSED does not protect against increased intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anesthesia.

Information for patients: Communicate the following information and instructions to the patient when appropriate: 1. Inform your physician about any alcohol consumption and medicine you are now taking, including nonprescription drugs. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous increasing of elochol and baryactionselipse. 2. Inform your physician if pour and protections in the patients of elochol and baryactionselipse. ingestion of alcohol and benzodiazepines. 2. Inform your physician if you are

VERSED* (midazolam HCI/Roche) INJECTION

pregnant or are planning to become pregnant. 3. Inform your physician if you are nursing

are nursing. Drug Interactions: The sedative effect of IV VERSED is accentuated by pre-medication, particularly narcotics (e.g., morphine, meperidine, fentanyl) and also secobarbital and innovar (fentanyl and droperidol). Consequently, adjust the dosage according to the type and amount of premedication. A moderate reduction in induction dosage requirements of thiopental (about 15%) has been noted following use of IM VERSED for premedication. IV administration of VERSED decreases the minimum alveolar concentration (MAC) of halothane required for general anesthesia. This decrease correlates

(MAC) of halothane required for general anesthesia. This decrease correlates with the dose of VERSED administered. Atthough the possibility of minor interactive effects has not been fully studied, VERSED and pencuronium have been used together in patients without noting clinically significant changes in dosage, onset or duration. VERSED does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium, or against the increased intracranlal pressure noted following administration of succinylcholine. VERSED does not cause a clinically significant change in dosage, onset or duration of a single intubating dose of succinylcholine.

No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atrooline, scopolamine,

drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, d-tubocurarine, succinylcholine and nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, dyclonine HCl and Cetacaine) have been observed.

Drug/laboratory test interactions: Midazolam has not been shown to Interfere with clinical laboratory test results.

Carcinogenesis, mutagenesis, impairment of fertility: Midazolam maleate was

administered to mice and rats for two years. At the highest dose (80 mg/kg/day) female mice had a marked increase in incidence of hepatic tumors and male rational into a had a manage increase in benign thyroid folloular cell tumors. These tumors were found after chronic use, whereas human use will ordinarily be of single or several doses.

Midazolam did not have mutagenic activity in tests that were conducted. A reproduction study in rats did not show any impairment of fertility at up to the times by dose.

A reproduction study in rais did not show any impairment of remains at up to ten times the human IV dose.

Pregnancy: Teratogenic effects: Pregnancy Category D. See WARNINGS section. Midazolam maleate injectable, at 5 and 10 times the human dose, did not show evidence of teratogenicity in rabbits and rats.

Labor and delivery: Use in obstetrics has not been evaluated. Because midaged in teratogenical teratogenical descriptions and because this production.

zolam is transferred transplacentally and because other benzodiazepines given in the last weeks of pregnancy have resulted in neonatal CNS depression, VERSED is not recommended for obstetrical use.

Nursing mothers: It is not known whether midazolam is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when injectable VERSED is administered to a nursing woman. Pediatric use: Safety and effectiveness in children below the age of 18 have

Pediatric use: Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS: See WARNINGS concerning serious cardiorespiratory events and possible paradoxical reactions. Fluctuations in vital signs following parenteral administration were the most frequently seen findings and included decreased tidal volume and/or respiratory rate decrease (23.3% of patients following IV and 10.8% of patients following IN administration) and apnea (15.4% of patients following IV administration), as well as variations in blood pressure and pulse rate.

Following IM injection: headache (13%): local effects at IM site: pain (3.7%).

tion) and apnea (15.4% of patients following IV administration), as well as variations in blood pressure and pulse rate. Following IM Injection: headache (1.3%); local effects at IM site: paln (3.7%), induration (0.5%), redness (0.5%), muscle stiffness (0.3%). Following IV administration: hiccoughs (3.9%), nausea (2.8%), vomiting (2.6%), coughing (1.3%), "oversedation" (1.6%), headache (1.5%), drowsiness (1.2%); local effects at the IV site: tenderness (5.6%), pain during injection (5.0%), redness (2.6%), induration (1.7%), phiebitis (0.4%). Other effects (<1%) mainly following IV administration: *Respiratory: Laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnea. *Cardiovascular:* Bigerniny, premature ventricular contractions, vasovagal episode, tachycardia, nodal rhythm. *Gastrointestinal:* Acid taste, excessive salivation, retching. *CNS/Neuromuscular:* Retrograde amnesla, euphoria, confusion, argumentativeness, nervousness, anxiety, grogginess, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, dreamling during emergence, sleep disturbance, insomnia, nightmares, athetoid movements, ataxia, dizziness, dysphoria, slurred speech, dysphonia, paresthesia. *Special Sense: Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyellds, visual disturbance, difficulty focusing eyes, ears biocked, loss of balance, lightheadedness. *Integumentary: Hives, hive-like elevation at injection site, swelling or feeling of burning, warmth or coloness at Injection site, rash, pruritus. *Miscellaneous: Yawning, lethargy, chills, weakness, toothache, faint feeling, hematoma. *Drug Abuse and Dependence: Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse potential is at least equivalent to that of diazepam. and dependence potential of midazolam suggest that its abuse potential is at least equivalent to that of diazepam.

OVERDOSAGE: Manifestations would resemble those observed with other benzodiazepines (e.g., sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma, untoward effects on vital signs). No specific

tion, diminished reflexes, coma, untoward effects on vital signs). No specific organ toxicity would be expected.

DOSAGE AND ADMINISTRATION: VERSED is a potent sedative agent which requires slow administration and individualization of dosage. Clinical experience has shown VERSED to be 3 to 4 times as potent per mg as diazepam. BECAUSE SERIOUS AND LIFE-THREATENING CARDIORESPIRATORY ADVERSE EVENTS HAVE BEEN REPORTED, PROVISION FOR MONITORING, DETECTION AND CORRECTION OF THESE REACTIONS MUST BE MADE FOR EVERY PATIENT TO WHOM VERSED INJECTION IS ADMINISTERED, REGARDLESS OF AGE OR HEALTH STATUS. Excess doses or rapid or single bolus intravenous administration may result in respiratory depression and/or arrest. (See WARNINGS.) Prior to use refer to the DOSAGE AND ADMINISTRATION section in the complete product information.

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The Dutch Guilder (Dfl.) price is definitive. U.S. \$ prices are subject to exchange rate fluctuations. Prices are exclusive B.T.W. for Dutch residents.

How to talk about drug abuse in the presurgical interview



ASK your patients if they use illegal drugs. Explain the possible effects of interactions with OR medications, and the long-term health risks of drug abuse.

LOOK for signs of drug abuse: avoidance of eye contact, increased motor activity, compulsive behavior, extreme nervousness, or dilation of the pupils.

LISTEN closely for answers such as "Well, I do drugs sometimes."

JUDGE NOT. Be candid and forthright, and not condescending, and you will encourage your patients to be honest.

PARTNERSHIP FOR A DRUG-FREE AMERICA

CHAIRPERSON: DEPARTMENT OF PEDIATRIC ANESTHESIA. CHILDREN'S MEMORIAL HOSPITAL, NORTHWESTERN UNIVERSITY MEDICAL SCHOOL, CHICAGO, ILLINOIS

Nationally recognized, 256 bed free-standing pediatric hospital seeks board certified anesthesiologist with academic leadership and administrative skills to run a department staffed with 14 board certified pediatric anesthesiologists and 4 CRNA's. Approximately 10,500 cases a year including all facets of pediatric anesthesia plus a 2 operating room surgicenter in one of the Western Suburbs. The candidate will be responsible for maintaining a successful teaching program, and developing a research program in basic sciences in a soon to be available new research building. The candidate should have extensive clinical experience in pediatric anesthesia, a proven record of scholarly activity and a commitment to graduate medical education. The candidate will hold an appropriate academic rank at Northwestern University Medical School. The candidate will assume the presidency of an already existing professional corporation which is responsible and is part of The Children's Memorial Faculty Practice Plan, Inc. Starting date will be January 1,

Applications accompanied by a detailed curriculum vitae and names of two individuals well known in academic circles for references should be directed to:

Frank Gonzales-Crussi, M.D. Chairman of Search Committee Department of Pathology Children's Memorial Hospital 2300 Children's Plaza Chicago, IL 60614

An equal opportunity/affirmative action employer



Jefferson Medical College

Senior Faculty at Associate Professor or Professor level to head a well established multidisciplinary Pain Center with a broad referral base. Beautiful modern 6500 sq. ft. facility with over 350 visits per month. Applicant must have at least 5 years practice experience in chronic pain therapy, the ability to manage a large facility with several faculty members, teaching, and research interests.

Interested individuals should send CV and references to:

Joseph L. Seltzer, M.D.
Professor & Chairman
Department of Anesthesiology
Thomas Jefferson University
Philadelphia, PA 19107-5092

TJU is an affirmative action/equal opportunity employer.



August 30-September 2, 1991 La Costa Spa and Resort Carlsbad, California

SECOND INTERNATIONAL Cardiac, Thoracic, and Vascular Anesthesia Update and Review

Accredited by
The Mount Sinai School of Medicine
in cooperation with

Journal of Cardiothoracic and Vascular Anesthesia (JCTVA) and the World Association of Cardiac, Thoracic, and Vascular Anesthesia

Faculty: Jonathan L. Benumof, M.D.
Joel A. Kaplan, M.D.
John Murkin, M.D.
Michael F. Roizen, M.D.
George Silvay, M.D., Ph.D.
Gerald D. Buckberg, M.D.
(JCTVA Honored Lecturer)

For further information:

Anita V. Guffin, M.M.S. Program Coordinator CT-ANES

P.O. Box 287 Port Chester, NY 10573 (212) 241-8392

ANESTHESIOLOGY

Board Certified/Eligible Anesthesiologist needed as Associate in Section of Anesthesia of 215 member multi-specialty clinic which serves as a referral center for surrounding areas of Northeastern Pennsylvania and the Southern Tier of New York State.

State-of-the-art facility. Medical school teaching affiliation through surgical residency program provides a stimulating environment. Tertiary Care Center performing 10,000 anesthetic procedures per year. Most types of surgery performed with emphasis on cardiovascular and neurosurgery.

Area provides attractive living conditions and many summer and winter recreational activities readily available. Easy access to major metropolitan areas. Excellent salary and fringe benefits. Respond with curriculum vitae to:

Guthrie Clinic Sayre, PA 18840 (717) 888-5858

ATTN: G. V. Ippolito Vice President

Classified Advertising

MAINE

BC or BE MD to join group of three MD anesthesiologists and four CRNAs in the practice of anesthesia, intensive care, and respiratory care. Phone (207) 622-1959 from 8:30 AM to 3:30 PM. Write to Chief of Anesthesia, Kennebec Valley Medical Center, 6 East Chestnut Street, Augusta, ME 04330.

560L/F

OHIO

Anesthesiologist, University Hospitals. Must be at least board eligible. Equal Opportunity, Affirmative Action Employer. Send curriculum vitae to Helmut F. Cascorbi, MD, PhD, Professor and Chairman, Department of Anesthesiology, University Hospitals of Cleveland, 2074 Abington Road, Cleveland, OH 44106.

571A/F

ILLINOIS, CHICAGO

Anesthesiologist BC/BE to join expanding group practice limited to outpatient anesthesia. Excellent opportunity for growth. Send CV to Marc Sloan, MD, 25 East Washington, Suite 300, Chicago, IL 60602.

574A/F

CALIFORNIA

The UCLA Department of Anesthesiology has openings for faculty with experience in anesthesia for organ transplantation. Requisites include clinical and teaching skills; eligibility for a California medical license; ABA certification or in process. Address correspondence with names of five references and curriculum vitae to Stuart F. Sullivan, MD, Department of Anesthesiology, UCLA School of Medicine, Los Angeles, CA 90024-1778. UCLA is an Affirmative Action, Equal Opportunity Employer.

584A/F

Cardiac anesthesiologists and Director of Obstetric Anesthesiology sought for academic medical center practice. Candidates for obstetric position must have experience in all types of obstetric anesthesia. Interest in research and teaching highly desirable. Present staff of 25 MDs, over 40 CRNAs, and over 20 residents provides challenging anesthesia care team setting. OR area contains state-of-the-art equipment in 20 new or renovated suites. Interested applicants should send CV and three references to Dr. Philip Lumb, Professor and Chairman, Al-

bany Medical College, Department of Anesthesiology, Code A-131, Albany, NY 12208. EOE.

592B/F

FLORIDA

BC/BE anesthesiologist for expanding ambulatory group practice. Part time/full time with no nights, emergencies, OB, or weekends. Please reply to Box 621C/H.

621C/H

PENNSYLVANIA

Immediate opening for BC/BE anesthesiologist to join 2 MDs and CRNAs in PA. Fee for service. Call Dr. Shah, (717) 242-7186, 9 AM to 5 PM.

623CDEF

ILLINOIS

Anesthesiologist to join congenial group of MDs/CRNAs expanding to provide anesthesia coverage for only hospital in city since recent merger. No open heart or neurosurgery. Environment conducive to family living, variety of schools, recreation. Good opportunity with stable future. City located in east central Illinois with population of approx. 40,000 (35 mile radius service area with 126,126 population). Within driving distance of Chicago and Indianapolis. Please send CV to Box 624C/H.

624C/H

ALABAMA—ANESTHESIOLOGIST

Faculty position for clinical BC/BE anesthesiologist at University of Alabama at Birmingham, Department of Anesthesiology. Opportunities to do clinical research, variety of clinical cases including liver transplantation. Desire to participate in teaching necessary. Limited night call. Generous benefit package. Salary competitive with private practice situations. Located in downtown Birmingham; city rated "America's most livable city" by U.S. Conference of Mayors, June 1989, and rated by Newsweek, February 1989, as "one of the nation's top 10 hot cities." Please contact Simon Gelman, MD, PhD, Professor and Chairman, Department of Anesthesiology, University of Alabama at Birmingham, 619 South 19th Street, Birmingham, AL 35233, (205)934-4696. An Affirmative Action/Equal **Employment Opportunity Employer**

626C/F

FULL-TIME ANESTHESIOLOGIST

BC or BE to join a group of anesthesiologists and CRNAs providing all types anesthesia coverage, though little obstetrical, to three hospitals and a day surgery facility in a southwest Louisiana city of approximately 75,000. Please send CV to Lake Charles Anesthesiology, 1415 18th Street, Lake Charles, LA 70601.

634C/H

ANESTHESIOLOGY CA-4 CRITICAL CARE MEDICINE

CA-4 training in Critical Care Medicine satisfying the requirement for certification of specialty competence in critical care medicine through anesthesiology. Newly approved program at the Albany Medical Center. Two positions available for July 1991. Send CV to Carol Kiner, Albany Medical Center, Anesthesia A-131, Albany, NY 12208.

631D/G

CLASSIFIED ADS

Anosthosia and Analgesia makes available classified advertising space for those interested in obtaining positions or wishing to announcements, postgraduate courses, or other pertinent events. We require that all advertisements be relevant to the practice of anesthesia and analgesia, and we reserve the right to refuse advertisements that are not relevant.

Specifications. Ads should be typewritten on the phase determines that the text bound be deadled.

Specifications. Ads should be typewritten on letterhead stationery; the text should be double-spaced, with the title or key phrase typed in capital letters. Enclose two photocopies with each ad. Display space (minimum ¹/₄ page) is available through Pharmaceutical Media, Inc., 440 Park Avenue South, 14th floor, New York, NY 10016, telephone. (212) 685-5010, FAX. (212) 685-6126.

Rates. Ads cost \$1.25 per word per insertion, with a minimum of 20 words. Abbreviations, dates, initials, post office box numbers, telephone numbers, vears, and zip codes are considered one word each. There is an additional fiee of \$17.00 per insertion for box number ads.*

fee of \$17.00 per insertion for box number ads.*

Payment. Full payment or institutional purchase order must accompany the copy for each ad. Ads received without a check or purchase order will be returned. (Make checks payable to Flsovier Science Publishing Company, Inc.)

order will be returned. (Make checks payable to Elsevier Science Publishing Company, Inc.)

Deadline. Copy must be received 7 weeks before publication date (i.e., by January 1 for the March issue); multiple-insertion ads are welcome. Ads may run up to 6 months per purchase order/payment. Please specify in which issue(s) your advertisement is to appear.

Send all add cony, payments, and correspon-

Send all ad copy, payments, and correspondence to: Austhesia and Analgesia Classified Ads. Desk Editorial, Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas. New York, NY 10010.

*When responding to a box number ad, include the box number on all correspondence.

ANESTHESIOLOGIST

Board certified/eligible to join expanding small group practice. Experienced in all anesthesia techniques including epidural block and pain management. No open heart or neurosurgery. Good opportunity for growth. Please send CV to Mount Vernon Anesthesia Associates, Box 391, Mount Vernon, OH 43050.

633D/F

MICHIGAN

ANESTHESIOLOGIST

Expanding surgery load results in opening of attractive permanent position for BC/BE "Team Player" in four-person fee-for-service practice in friendly four-season recreational, lakeside community. Share call and 3800 cases annually at 174-bed hospital. Little OB, no OH or neuro. Send inquiries and CV to Stephanie Riemer, Mercy Hospital, 400 Hobart Street, Cadillac, MI 49601, or call (616) 779-7404.

Department of Anesthesiology at the

SUNY Health Science Center in Syracuse,

N.Y. is recruiting faculty at the instructor

and assistant and associate professor lev-

els. Qualified individuals with a strong

academic commitment in all types of anesthesia, critical care, and pain management are sought. SUNY Health Science Center is

a tertiary care center and provides clinical

services also to the Syracuse Veterans Ad-

ministration Hospital. Rank and salary are

commensurate with experience. Must be

board certified or board eligible and pos-

sess a New York State medical license.

Please send letter, curriculum vitae, names,

addresses, and phone numbers of three

references to Enrico M. Camporesi, MD,

Professor and Chairman, Department of

Anesthesiology, SUNY Health Science

Center, Syracuse, NY 13210. The State Uni-

versity of New York Health Science Center

is an Equal Opportunity/AA Employer.

range of surgeries at two community hos-

pitals. No open heart. Picturesque central

Maine location near lakes, mountains, and

ocean. Referral area of 75,000+. Competi-

tive compensation package. Contact Jill

Gilbert at (207) 872-1136 or send CV to

Waterville Anesthesia Associates, 44 Main

Street, Waterville, ME 04901.

645D/F

643D/G

NORTHERN NEW ENGLAND

Chief and/or Staff Anesthesiologist, BC/BE for 194-bed VA Medical Center, fully affiliated with Dartmouth-Hitchcock Medical Center and Dartmouth Medical School. Active teaching hospital. Academic appointment and salary commensurate with experience. Part-time position a possibility. Good schools, cultural offerings, beautiful country environment, good skiing, excellent book store. Two and a half hours from Boston, Massachusetts-one and a half hours from Burlington, Vermont. For further information, call John M. Head, MD, Chief of Surgery, or Susanne Learmonth, Acting Chief of Anesthesia, (802) 295-9363, extension 5290, or FTS 834-1290, or send CV to above at VA Medical Center, White River Junction, VT 05001. EOE/MF.

635D/F

PEDIATRIC ANESTHESIA

Due to expansion of our clinical responsibilities, positions are available for pediatric anesthesiologists at Arkansas Children's Hospital. We provide primary and tertiary care for children locally and in six surrounding states. We are especially interested in those with special training or experience in pediatric cardiovascular anesthesia and pain management. Please send replies to Raeford E. Brown, Jr., MD, Chief, Division of Pediatric Anesthesia, Arkansas Children's Hospital, 800 Marshall Street, Little Rock, AR 72202-3591. An Equal Opportunity Employer.

636D/F

STAFF MDA

Need ASAP or 7/91. Midwest Metro, 399 beds, BE/BC. Includes heart-OB-pain. Relaxed, excellent work/living environment. Send CV to A.M.I., P.O. Box 2153, Shawnee Mission, KS 66201.

640D/F

MOUNTAIN SOUTHWEST

Anesthesia care team in level II trauma center seeks anesthesiologists and CRNAs for full-time and part-time positions. Reply in confidence to Box 642D/F.

642D/F

MAIN

Anesthesiologist needed to join five-anesthesiologists, 10-CRNA group doing wide

Anesthesiologist with experience and expertise in acute and chronic pain management is sought to establish a pain management service for both inpatients and outpatients. Ours is a large group practice in the mountains of the southeastern U.S. Compensation and benefits will be commensurate with training, experience, and board certification. Reply to Box 653D/G.

CALIFORNIA

The UCLA Department of Anesthesiology is searching for a faculty person with experience in ophthalmologic anesthesia to be Chief of the Ophthalmologic Anesthesia Division. Candidates are required to show evidence or promise of research productivity and scholarly writing. Other requisites

include clinical and teaching skills, commitment to discovery, eligibility for a California medical license, ABA certification. Address correspondence with names of five references and curriculum vitae to Thomas M. Grove, MD, PhD, Department of Anesthesiology, UCLA School of Medicine, Los Angeles, CA 90024-1778. UCLA is an Affirmative Action, Equal Opportunity Employer.

654D/F

UNIVERSITY OF PENNSYLVANIA

Anesthesiology Research Training: Applications are invited for 2 years full time in an NIH funded, Training for Anesthesia Research program. The specific program (and areas of training) is individually designed to meet the needs of each trainee and is usually a mix of course work and laboratory or clinical research activities. The research training is coordinated between the Department of Anesthesia and the chosen basic science field. For information write (include current CV) to Bryan E. Marshall, MD, FRCP, Director, Training for Anesthesia Research Program, 781 Dulles, Department of Anesthesia, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104.

657D/F

MUSKEGON, MICHIGAN

Private anesthesia group seeking anesthesiologists to join a seven-man group of physicians employing five CRNAs. We practice in two hospitals with a total capacity of 600–700 beds. All specialty modalities represented. If interested, please write to Frederick Wakerley, DO, or Carsten Boysen, MD, 1060 West Norton Avenue, Muskegon, MI 49441.

659E/G

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652D/F

BC/BE, to join growing group of anesthesiologists and CRNAs at 475-bed, university-affiliated hospital on Ohio's North Coast. All types of surgery except organ transplantation. Send CV to North Coast Anesthesiologists, 11311 Shaker Boulevard, Cleveland, OH 44104.

660E/G

MISSISSIPPI: ANESTHESIOLOGY FACULTY, UNIVERSITY OF MISSISSIPPI MEDICAL CENTER

Major reorganization and expansion of academic department under new chairman creates opportunities at all levels, instructor to professor, for generalists and for subspecialists with training and/or experience in pediatric, obstetric, cardiac, neuro, and ambulatory anesthesia, intensive care, and pain management (acute and chronic). Active clinical and didactic resident teaching required. Clinical and laboratory research

possible and encouraged; space and start-up funds available. A wealth of interesting and challenging clinical cases comes from statewide referrals. Also need for a clinical director with some administrative (OR/schedule/personnel) experience. All positions require eligibility for Mississippi licensure. ABA certified or examination process. Rank and academic salary determined by qualifications. Generous practice compensation. Remarkably pleasant and affordable living in Jackson, the urban "Bold New City" of the South, a state capital with a metropolitan area population of over 400,000, outstanding schools, culture, and recreation/outdoor activities. Please forward inquiry and CV to John H. Eichhorn, MD, Professor and Chairman, Department of Anesthesiology, The University of Mississippi Medical Center, 2500 North State Street, Jackson, MS 39216-4505. An equal opportunity employer, M/F/H/V 662E/G

CHAIR: DEPARTMENT OF ANESTHESIOL-OGY, THE UNIVERSITY OF TEXAS MEDICAL **BRANCH AT GALVESTON**

Applications and nominations are invited for the position of Chair of the Department of Anesthesiology. Candidates must be highly qualified with nationally recognized credentials in research and senior academic accomplishments with administrative experience or potential. The position offers excellent opportunity to develop an internationally leading academic department with outstanding resources, scientific environment, and faculty positions.

Application or nomination should include a curriculum vitae. Address correspondence to Courtney M. Townsend, Jr, MD, Robertson-Poth Professor, Department of Surgery, The University of Texas Medical Branch, Galveston, TX 77550. The University of Texas Medical Branch is an Affirmative Action/Equal Opportunity Emplover.

663EF

BC/BE anesthesiologist for a 500-bed tertiary hospital in a Florida coastal city. Immediate opening. Liberal salary and early partnership. Send resume to Box 664EF.

664EF

ADIRONDACK-LAKE CHAMPLAIN RE-**GION**

Upstate New York-growing, active department seeks additional BC/BE anesthesiologist. Limited OB, neuro, and pediatrics; no open heart. Excellent starting salary. Close to Montreal and the Olympic-Lake Placid region. If you enjoy skiing and sailing, contact us for more details: Hannah Hanford, P.O. Box 1656, Plattsburgh, NY 12901; (518) 643-2998.

665E/H

OHIO STATE UNIVERSITY, COLUMBUS

The Department of Anesthesiology, due to program expansion, is recruiting for CA-3 (PGY IV) housestaff positions for July 1, 1991 through June 30, 1992. OSU is a 1000bed regional referral, Level I Trauma and Burn Center. Rotations are available in obstetric anesthesia, advanced clinical track, pediatric anesthesia, SICU/critical care, and research. For further information contact Residency/Education Coordinator, Department of Anesthesiology, The Ohio State University Hospitals, N-429 Doan Hall, 410 West Tenth Avenue, Columbus, OH 43210.

The University of New Mexico Department of Anesthesiology is recruiting a VA Chief of Service for its department at the New Mexico Regional Medical Facility (VA Hospital) in Albuquerque. Requirements include proven administrative, teaching, and leadership abilities, academic experience, and board certification. Appointment will be at the associate or full professor level. Qualified candidates should contact Jorge Estrin, MD, PhD, Chairman, Department of Anesthesiology, University of New Mexico School of Medicine, 2211 Lomas Boulevard, N.E., Albuquerque, NM 87106; (505) 843-2610. The University of New Mexico is an Equal Opportunity, Affirmative Action Employer.

670EF

The University of New Mexico Department of Anesthesiology is recruiting faculty for the following: (1) Obstetrical Anesthesia at the assistant, associate, or full professor rank. (2) Critical Care Medicine at the assistant or associate level. It is expected that candidates for CCM positions will have or be eligible for subspecialty certification. Faculty responsibilities include provision of clinical care, teaching, and research. Qualified candidates should send a CV or contact lorge Estrin, MD, PhD, Chairman, Department of Anesthesiology, University of New Mexico School of Medicine, 2211 Lomas Boulevard, N.E., Albuquerque, NM 87106; (505) 843-2610. The University of New Mexico is an Equal Opportunity, Affirmative Action Employer.

671EF

lowship experience. Interested individuals should contact Jorge Estrin, MD, PhD, Professor and Chairman, Department of Anesthesiology, University of New Mexico, 2211 Lomas Boulevard, N.E., Albuquerque, NM 87106; (505) 843-2610. The University of New Mexico is an Equal Opportunity, Affirmative Action Employer.

672EF

POSTDOCTORAL FELLOWSHIP

Background in clinical medicine or clinical research required for studies with patients with heart disease undergoing surgery. Cardiac function and ischemia assessed with ECG, Holter, and echocardiography monitoring. Working with cardiologists, epidemiologists, and anesthesiologists. Send CV and names of three references to Dennis T. Mangano, PhD, MD, Professor and Vice Chairman, Department of Anesthesia, University of California, San Francisco, 4150 Clement Street (129), San Francisco, CA 94121.

674E/D

ACADEMIC CRITICAL CARE PEDIATRICIAN Children's Hospital Medical Center, Cincinnati, Ohio, a 350-bed University-affiliated teaching hospital, is seeking a fulltime director of pediatric critical care. Candidates should be eligible for academic appointment at the associate professor or professor level at the College of Medicine at the University of Cincinnati. Applicants must be board certified or board eligible in pediatric critical care medicine or possess equivalent qualifications. Responsibilities include direction of the clinical program which has 27 beds and includes a cardiac care unit, a general unit, and isolation facilities; and direction of a pediatric critical care fellowship program. It is anticipated that the successful candidate will have demonstrated productivity in clinical or basic research. Forward applications to Robert W. Wilmott, MD, Chairman, ICU Search Committee, Children's Hospital Medical Center, Elland and Bethesda Avenues, Cincinnati, OH 45229-2899. Children's Hospital Medical Center is an Equal Opportunity, Affirmative Action Employer.

676FF

CARDIOVASCULAR FELLOWSHIP OPPOR-TUNITY

The Department of Anesthesiology at the University of New Mexico School of Medicine has openings at the CA-4 level for advanced training in cardiovascular anesthesiology. The fellowship is a 2-year, comprehensive program designed to train the fellow for a career in cardiovascular anesthesiology. Research in cardiovascular physiology and anesthesia, provision of clinical care for complex adult and pediatric cases, participation in conferences, and teaching responsibilities are part of the fel-

SITUATION WANTED

U.S. born—U.S. trained—board certified in pain management. Will complete Pain Management Fellowship in July 1991. Desires anesthesia practice with strong emphasis on pain management. Prefer West Coast. Will consider western United States. Age 42. Twelve years private practice experience. Call (913) 681-8543 evenings only (central time zone), or reply to box 677EF.

677EF

CALIFORNIA ANESTHESIOLOGIST(S)

The Department of Anesthesia, University of California, San Francisco, seeks candidates at the assistant or associate level(s) for teaching and clinical responsibilities at the Veterans Administration Hospital in San Francisco. Candidates must have training in clinical cardiovascular research. The ongoing research studies are multidisciplinary and multicenter, addressing perioperative ischemia and morbidity. The University of California is an Equal Opportunity Affirmative Action Employer. Please forward curriculum vitae and three references to Ronald D. Miller, MD, Professor and Chairman, or, Dennis Mangano, MD, PhD, Professor, Department of Anesthesia, UCSF, 521 Parnassus Avenue, Box 0648, Room C-455, San Francisco, CA 94143-

682EF

PAIN MANAGEMENT FELLOWSHIP

The Pain Consortium of Greater Kansas City is offering a 12-month fellowship in pain management. This is a unique training opportunity for a highly motivated, patient-oriented anesthesiologist to participate in a strong clinical pain management program. Emphasis is on comprehensive evaluation and the use of neural blockade in the treatment of acute, chronic, and cancer pain. Training in interventional pain management techniques including implantable drug delivery systems and CT-guided neurodestructive procedures is integrated with strong individual clinical teaching.

Applicant must possess strong interest in regional anesthesia and desire one-on-one patient contact. NO OR or OB anesthesia responsibilities. Applicant MUST be BC/BE in anesthesia prior to beginning training. Applicants should send CV and three (3) letters of recommendation to Pain Consortium of Greater Kansas City, 11111 Nall #202, Leawood, KS 66211.

683E/G

Immediate positions available for part-time anesthesiologists, Monday through Friday, 7:00 am to 3:30 pm (no call), to join a group of 17 anesthesiologists and 11 CRNAs in Northwestern Indiana, 35 min from downtown Chicago. Excellent compensation package. Contact (219) 922-6366 or send curriculum vitae to Box 684F/I.

684F/I

NEW ORLEANS, LOUISIANA SUBURB; McALLEN, TEXAS; CHICAGO, ILLINOIS! Join established anesthesiologists in private practice. Excellent opportunities with busy physicians. For details, call Eloise Gusman, 1-800-535-7698 or send CV to P.O. Box 1685, Covington, LA 70434-1685.

685/F

Certified registered nurse anesthetist needed for 115-bed VA Medical Center in western Colorado. Anesthesia staff consists of two CRNAs and one anesthesiologist. Surgeries include general, noncardiac thoracic, peripheral vascular, orthopedics, urology, and ENT. Special salary rates approved. Send CV to Dr. Mary Mastin, Chief, Surgical Service (112), VA Medical Center, 2121 North Avenue, Grand Junction, CO 81501 or call (303) 242-0731, extension 2419. EOE.

686FG

DEPARTMENT OF ANESTHESIOLOGY, MEDICAL UNIVERSITY OF SOUTH CAROLINA, CHARLESTON is recruiting for three faculty positions. One position requires expertise in Critical Care. The two other positions are for general staff anesthesiologists. All three positions involve clinical duties, teaching responsibilities, and research opportunities. Academic appointment based on credentials. Please respond with CV to John E. Mahaffey, MD, Professor and Chairman, Department of Anesthesiology, Medical University of South Carolina, 171 Ashley Avenue, Charleston, SC 29425-2207.

687F

FELLOWSHIP—CARDIAC ANESTHESIOLOGY CA3 or 4 fellowship position available July 1991 in cardiac anesthesia. Busy open heart and vascular service. Opportunity for OR, cath lab, ICU, and clinical research. Excelent salary/benefit package. Send inquiries with CV to Anthony A. Ascioti, MD, Department of Anesthesiology, St. Joseph's Hospital Health Center, 301 Prospect Avenue, Syracuse, NY 13203.

688FG

PENNSYLVANIA

The Albert Einstein Medical Center is seeking a Director of Cardiac Anesthesia and one additional cardiac anesthesiologist. Approximately 800 adult hearts per year. Interest in teaching and clinical research required. Potential for laboratory research. Modern 600-bed tertiary hospital. Fully accredited residency. Major affiliate of Temple University. Very attractive financial package. Interested applicants should reply to Jonathan Roth, MD, Department of Anesthesiology, Albert Einstein Medical Center, 5501 Old York Road, Philadelphia, PA 19141; (215)456-7979.

689FG

PENNSYLVANIA

The Albert Einstein Medical Center has one faculty position available. Approximately 50% in Pain Management. Responsibility will include clinic visits and postoperative pain management. Interest in teaching and clinical research required. Over 12,000 anesthetics performed annually. Modern 600-

bed tertiary hospital. Fully accredited residency. Major affiliate of Temple University. Interested applicants should send a CV to Jonathan Roth, MD, Department of Anesthesiology, Albert Einstein Medical Center, York and Tabor Roads, Philadelphia, PA 19141; (215)456-7979.

690FG

Anesthesiologists needed at assistant, associate, and professor levels. Must be board certified or board eligible. Duties include patient care, resident and medical student teaching, and research. Positions available at the University of Missouri-Columbia Health Sciences Center. Interested applicants send curriculum vitae to G.W.N. Eggers, Jr, MD, Anesthesiology, University of Missouri Health Sciences Center, Columbia, MO 65212.

691F/H

ANESTHESIOLOGIST/FLORIDA.

Excellent starting opportunity, unexpected position available, July 1991. Growing 100-bed hospital in suburban community, 30 minutes north of Tampa Bay. Full partnership in 3 years. BE/BC. PO Box 1166, Dade City, FL 33525. (813)788-0411, Ext. 2315 or (813)782-0285.

692F

LOOKING FOR ANESTHESIOLOGIST

Join growing lake community of 50,000 just 30 minutes from metropolitan center of 1 million in Midwest. Partnership level \$400,000.00 plus; early partnership. 7500 Cases annually growing by 10% per year; 10 hospital-employed nurse anesthetists. Good hours, very congenial surgeons and good working environment, brand-new anesthesia machines, profitable and growing hospital. Apply to Box 693F.

693F

ARKANSAS

Immediate opening available for BC/BE anesthesiologist in NW Arkansas. 240-Bed hospital. Busy fee-for-service practice with congenial group. Send CV and references to Linda Hall, 216-A North Greenwood, Fort Smith, AR 72901.

694F

PEDIATRIC CARDIAC ANESTHESIOLOGIST

We are looking for an anesthesiologist with considerable experience in managing all types of pediatric cardiac surgery. The applicant needs to be an accomplished teacher with research interests in the field. Growing cardiac anesthesia practice with 1000 adult and over 150 pediatric cardiac interventions at a 500-bed tertiary care hospital in downtown Boston with 2500 general pediatric cases and three cardiac oper-

ating rooms. New England Medical Center and the Floating Hospital for Infants and Children are the primary affiliates of Tufts University School of Medicine. Qualified applicants should send CV with letter to W. Heinrich Wurm, MD, Acting Chairman, Department of Anesthesia, New England Medical Center, Box 298, 750 Washington Street, Boston, MA 02111.

695FG

EXPERIENCED CARDIAC/CHRONIC PAIN THERAPY

Board-certified anesthesiologist trained in major midwestern medical center looking for busy practice. Will consider all situations. CV and references available upon request. Please reply to Box 696F.

696F

A temporary position at the Research Assistant Professor level is available with a stipend of \$24,000 per year; position is contingent upon renewal of funding. The NIH-funded projects, for the study of molecular mechanisms of anesthesia, require knowledge of statistical mechanics, quantum chemistry, and mathematical technique of solving dynamical systems. The applicant should be fluent in computer languages and capable of setting up measurement circuits based on digital and analog techniques. Specific areas of research are in colloid science and micelle formation and physical properties of lipid bilayer vesicles and planar lipid membranes. Send application to Dr. K. C. Wong, Chairman, Department of Anesthesiology, University of Utah School of Medicine, 50 North Medical Drive, Salt Lake City, UT 84132. Closing date for this position is May 15, 1991 or until suitable applicant is identified. The University of Utah is an AA/EEO employer.

UNIVERSITY OF CALIFORNIA, SAN FRAN-CISCO, PAIN MANAGEMENT

Faculty positions available for board certified/eligible anesthesiologists whose primary clinical responsibilities would be in a well-organized Pain Management Center run by the Department of Anesthesia. This

position is available in the In Residence or Clinical series at the assistant, associate, or professor level. Must have at least 5 years of postgraduate training, including research or other clinical training. Duties to also include patient care, resident and medical student teaching, and research or specialized clinical activity. California medical icense required. Send correspondence, curriculum vitae, and list of professional referees to Ronald D. Miller, Professor and Chairman, UCSF, Department of Anesthesia, Box 0648, Room C-455, 521 Parnassus Avenue, CA 94143-0648. The University of California is an Equal Opportunity Employer.

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DESCRIPTION: ALFENTA is a sterile, non-pyrogenic, preservative free aqueous solution containing alfentanil hydrochloride equivalent to 500 µg per mi of alfentanil base for intravenous injection. The solution, which contains sodium chloride for isotoricity, has a pH range of 4.0-6.0.

CONTRAINDICATIONS: ALFENTA (alfentanil hydrochloride) is contraindicated in patients with known hyper-

CONTRAINDICATIONS: ALFENTA (altentanii hydrochloride) is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: ALFENTA SHOULD BE ADMINISTERED ONLY BY PERSONS SPECIFICALLY TRAINED IN THE USE OF INTRAVENOUS AND GENERAL ANESTHETIC AGENTS AND IN THE MANAGEMENT OF RESPIRATORY EFFECTS OF POTENT OPIOIDS. AN OPIOID ANTAGONIST, RESUSCITATIVE AND INTUBATION EQUIPMENT AND CXYGEN SHOULD BE READILY AVAILABLE. BECAUSE OF THE POSSIBILITY OF DELAYED RESPIRATORY DEPRESSION, MONITORING OF THE PATTENT MUST CONTINUE WELL AFTER SURGERY ALFENTA (aflentanii hydrochloride) administered in initial dosages up to 20 µg/kg may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is usually dose-related. Administration of ALFENTA at anesthetic induction dosages (above 130 µg/kg) will consistently produce muscular rigidity with an immediate onset. The onset of muscular rigidity occurs earlier than with other opioids. ALFENTA may produce muscular rigidity that involves all skeletal muscles, including those of the neck and extremities. The incidence may be reduced by: 1) routine methods of administration of heuromuscular blocking agent for balanced opioid anesthesia; 2) administration of up to ¼ of the full paralyzing dose of a neuromuscular blocking agent should be administered, or 3) simultaneous administered anesthetic dosages (above 130 µg/kg). The neuromuscular blocking agent when ALFENTA is used in rapidly administered anesthetic dosages (above 130 µg/kg). The neuromuscular blocking agent used should be appropriate for the patient's cardiovascular status. Adequate facilities be fully equipped to handle all degrees of respiratory depression.

PRECAUTIONS: DELAYED RESPIRATORY DEPRESSION, RESPIRATORY ARREST, BRADYCARDIA, ASYSTOLE. ARRHYTHMAS AND HYPOTENSION HAVE ALSO BEEN REPORTED. THEREFORE, UTALL SIGNS MUST BE MONITORED CONTINUOUSLY.

ERREAL The initial dose of ALFENTA (affentanii hydrochloride) should be appropriately in deferly and

PRECAUTIONS: DELAYED RESPIRATORY DEPRESSION, RESPIRATORY APPLAS (SIGN MUST BE MONITORED CONTINUOUSLY.

General: The initial dose of ALFENTA (alfentanil hydrochloride) should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. In obese patients (more than 20% above ideal total body weight, the dosage of ALFENTA fould be determining the state of the patients of the properties of the properties of the properties of the properties of delta waves in EEG, was do'ble lower in geriatric patients than that needed in healthy young patients. In patients with compromised liver function and in geriatric patients than that needed in healthy young patients. In patients with compromised liver function and in geriatric patients than that needed in healthy young patients. In patients with compromised liver function and in geriatric patients than that needed in healthy young patients. In patients with compromised liver function and in geriatric patients than that needed in healthy young patients. In patients with compromised liver function and in geriatric patients is than that needed in healthy young patients. In patients with compromised liver function and in geriatric patients is the plasma clearance of ALFENTA may be reduced and postoperative recovery may be prolonged. Induction doses of ALFENTA should be administered slowly (over three minutes). Administration may produce sos of variety of the minutes of the patients of the pat

respiration.

Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, ALFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of ALFENTA. Drug Interactions: Both the magnitude and duration of central nervous system and cardiovascular effects whe enhanced when ALFENTA kis administered in combination with other CNS depressants such as barbiturates, tranquilizers, opioids, or inhalation general anesthetics. Postoperative respiratory depression may be enhanced prolonged by these agents. In such cases of combined treatment, the dose of one or both agents should be reduced Limited clinical experience indicates that requirements for volatile inhalation anesthetics are reduced by 30 to 50% or the first sixty (60) minutes following ALFENTA induction. The concomitant use of erythromycin with ALFENTA: an significantly inhibit ALFENTA clearance and may increase the risk of prolonged or delayed respiratory depression in the processor of the

operative administration of drugs anectring nepatic blood live or enzyme function may reduce plasma containing or prolong recovery.

nogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of ALFENTA have refromed to evaluate carcinogenic potential. The micronucleus test in female rats and the dominant lethal sfemale and male mice revealed that single intravenous doses of ALFENTA as high as 20 mg/kg (approximately less the upper human dose) produced no structural chromosome mutations or induction of dominant lethal ions. The Ames Salmonella typhimurium metabolic activating test also revealed no mutagenic activity, nancy Category C: ALFENTA has been shown to have an embryocidal effect in rats and rabbits when given es 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects could have been due ernal toxicity (decreased food consumption with increased mortality) following prolonged administration of J. P. S. Laber and the studies of the proposition of the

Nursing Mothers: In one study of nine women undergoing post-partum tubal ligation, significant levels of ALFENIA were detected in colostrum four hours after administration of 60 μg/kg of ALFENIA, with no detectable levels present after 28 hours. Caution should be exercised when ALFENIA is administered to a nursibe woman. Pediatric Use: Adequate data to support the use of ALFENIA in children under 12 years of age are not presently

available

ADVERSE REACTIONS: The most common adverse reactions, respiratory depression and skeletal muscle rigidity, are extensions of known pharmacological effects of opioids. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity, Delayed respiratory depression, respiratory arest, tradycardia, asystole, arrhythmias and hypotension have also been reported. The reported incidences of adverse reactions listed in the following table are derived from controlled and open clinical trials involving 1183 patients, of whom 785 received ALFENTA The controlled trials involving whose the comparisons with fentanyl, thiopental sodium, enflurane, saline placebo and halothane. Incidences are based on disturbing and nondisturbing adverse reactions reported. The comparative incidence of certain side effects is influenced by the type of use, e.g., chest wall rigidity has a higher reported incidence in clinical trials of affentanil induction, and by the type of surgery, e.g., nausea and vomitting have a higher incidence in patients undergoing gynecologic surgery.

Percent	ALFENTA (N = 785)	Fentanyl (N = 243)	Thiopental Sodium (N = 66)	Enflurane (N = 55)	Halothane (N = 18)	Saline Placebo* (N = 18)
Gastrointestinal						
Nausea	28	44	14	5 9	0	22
Vomiting	18	31	11	9	13	17
Cardiovascular						
Bradycardia	14	7	8	0	0	0
Tachycardia	12	12	39	36	31	11
Hypotension	10	8	7	7	0	0
Hypertension	18	13	30	20	6	0
Arrhythmia	2	2	5	4	6	0
Musculoskeletal						
Chest Wall Rigidity	17	12	0	0	0	0
Skeletal Muscle Movements	6	2	6	2	0	0
Respiratory						
Apnea	7	0	0	0	0	0
Postoperative Respiratory Depression	2	2	0	0	0	0
CNS						
Dizziness	3 2	5 8	0	0	0	0
Sleepiness/ Postoperative Sedation	2	8	2	0	0	6
Blurred Vision	2	2	0	0	0	0

Blurred Vision 2 2 0 0 0 0

From two clinical trials, one involving supplemented balanced barbiturate / nitrous oxide anesthesia and one in healthy voluntheers who did not undergo surgery.

In addition, other adverse reactions less frequently reported (1% or less) were: Laryngospasm, bronchospasm, postoperative conflusion, headache, shivering, postoperative euphoria, hypercarbia, pain on injection, urticaria, and itching. Some degree of skeletal muscle rigidity should be expected with induction doses of ALFENTA, and induction doses of ALFENTA (alfentanii hydrochloride) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

VVERDOSABE: Overdosage would be manifested by extension of the pharmacological actions of ALFENTA (alfentanii hydrochloride) (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. No experience of overdosage with ALFENTA was reported during clinical trials. The intravengus LD₉₀ of ALFENTA is 43.0-50.9 mg/kg in rats, 72.2-73.6 mg/kg in mince, 71.8-819 mg/kg in guinea pips and 59.5-95.75 mg/kg in dogs. Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with ALFENTA may be longer than the duration of a controlled ventilation as indicated for hypoventilation or apnea. If respiratory depression is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled ventilations as indicated for hypoventilation of nanage hemodynamic instability.

be required to manage hemodynamic instability. DOSAGE AND ADMINISTRATION: The dosage of ALFENTA (alfentanil hydrochloride) should be individualized in each patient according to body weight, physical status, underlying pathological condition, use of other drugs, and type and duration of sugical procedure and another in other basis of the pathological conditions, use of other drugs, and weight), the dose of sugical procedure and another in other basis of the abody weight. The dose of ALFENTA should be reduced in elderly or delitated pathological procedure and the pathological conditions and the pathological conditions and the pathological conditions are described by the pathological conditions and the pathological conditions are discussed as a pathological condition and the pathological conditions are described by the pathological conditions are described

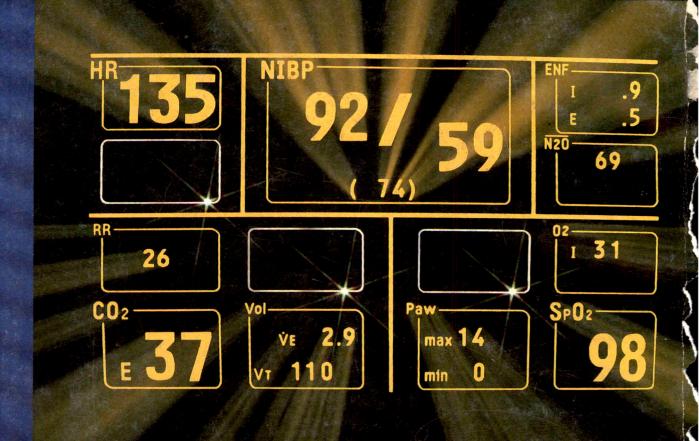
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